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CYSTIC DISEASE OF THE KIDNEYS *

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Small macroscopic cysts are found in a majority of adult kidneys and in a fair percentage of the kidneys of infants, and if thorough microscopic examinations are made the percentage with cysts is still greater. In a large postmortem service one finds all transitions from typical clinical polycystic kidneys, through subclinical polycystic kidneys to solitary cysts. The structural alterations vary with the number and size of the cysts. Clinical examples of polycystic kidney disease are, however, easily distinguished from clinical solitary cysts. A convenient anatomical classification of renal cysts is as follows:

I. Cystic disease (typical polycystic kidneys)
   (A) Bilateral cystic disease
      (1) clinical
         - large kidneys
         - normal sized kidneys
         - hypoplastic kidneys
      (2) subclinical
   (B) Unilateral cystic disease
      (1) large kidney
      (2) hypoplastic kidney
      (3) partial cystic degeneration

II. Large solitary cysts

III. Multiple small cysts associated with contracted kidneys

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Cystic Disease

This paper deals only with typical polycystic kidneys. The clinical group includes all those with severe degeneration of the kidneys, and in the adults there were always symptoms referable to the kidneys. The subclinical group includes enlarged kidneys filled with cysts but containing sufficient healthy parenchyma to maintain normal renal function. The lower limit of this group is arbitrary, but no case was included unless the cysts caused a definite enlargement of the kidney or replaced a large proportion of its parenchyma.

Frequency: The reported incidence of polycystic kidneys in postmortem examinations is shown in Table I. The greater frequency

Table I

Frequency of Polycystic Kidneys

Author	No. of polycystic kidneys	No. of postmortems	Ratio
Naumann	16	10,000	1:625
Preitz	16	10,000	1:625
Ward	40	14,000	1:350
Ssokoloff	192	50,000	1:260
Watson and Cunningham	10	2,429	1:243
Bugbee and Wollstein	13	4,903 (*children*)	1:377
Wakely	3	3,521	1:1173
Braasch and Schacht	9	9,171	1:1019
Bell	44	22,393	1:509

in some statistics is no doubt due in part to the inclusion of kidneys with only a few cysts. Thus Bugbee and Wollstein include in their group several cases which would be excluded by the more rigid criteria that we have employed, since there were only a few cysts. In this table unilateral polycystic kidneys are included as well as kidneys in which the replacement of parenchyma was not extensive enough to produce clinical symptoms. Of our 44 cases 4 were unilateral and 7 were subclinical; only 33 were advanced cases of bilateral polycystic kidneys.

The frequency in postmortem statistics is also influenced by the number of stillbirths and young infants that are included in the series. In 1819 stillbirths we found 8 examples of polycystic kidneys, and there were 6 cases in infants under 6 months of age. In 17,884

postmortems on individuals over 1 year of age there were 30 examples of polycystic kidneys, 1:596. There were 21 clinical cases in this group, 1:851. Braasch and Schacht found 1 clinical case in each 3523 admissions to the Mayo Clinic.

Unilateral Polycystic Kidney: Cases occur in which one kidney is normal while the other is indistinguishable from the typical bilateral type of the disease. The unilateral cystic kidney may be hypoplastic. Small kidneys measuring from 2 to 6 cm. in length have been reported by Schaefer, Herxheimer, Baumann (2 cases), and Rosenow. The very small kidneys composed of a few cysts are best classified as unilateral hypoplasia. Four cases of this type have come under our observation but have not been included as polycystic kidneys.

Sieber stated that 9 of 150 collected cases were unilateral, but the size of the cystic kidneys was not given. Wakely reported a unilateral cystic kidney, measuring 7 by 5 inches, in a child 20 months old.

Four of our 44 cases were large, unilateral polycystic kidneys, the respective weights being given in Table IV. These kidneys differ in no way from bilateral cystic kidneys. If the four hypoplastic cystic kidneys mentioned above be included, 8 of 48 cases are unilateral. Clinical reports of unilateral cystic kidneys are unreliable since they are usually examples of bilateral involvement with one kidney in a more advanced stage of the disease than the other.

Age: In the literature it is commonly stated that polycystic kidneys occur at two periods, *viz.* early infancy and adult life, and that there is a gap between these ages in which few or no cases occur. In cases collected from a large autopsy service this gap appears (Table II). In our records there is only 1 case between the ages of 4 months and 25 years, and this was unilateral. In clinical experience there are few cases before the third decade. A search of the literature, however, shows that a number of cases in the first and second decades have been recorded. Sieber, in 1901, collected 32 cases between the newborn period and the age of 20 years. In Table II the age distribution of 202 cases collected from the literature is shown. This is only a small fraction of the total cases reported, but perhaps the group is sufficiently large to show the general age distribution. No doubt the number of stillbirths is much too small in proportion to the other groups since these cases are seldom published. In our postmortems nearly one-third of the cases were in the newborn group.

The age recorded usually represents the time when the disease was first recognized either clinically or at postmortem, but in many instances the actual time of onset, as indicated by the symptoms, was many years before the diagnosis was established. Several writers, in studying families with hereditary polycystic kidney disease, have recognized cases in which no subjective symptoms had developed. When these facts are taken into consideration the newborn and the adult groups are brought closer together. There is no longer any

TABLE II

Age Distribution of Author's Cases and Cases Collected from the Literature

Age	Author's cases		Cases collected from literature
	Polycystic kidneys	No. of autopsies	
Stillborn	9 (1 unilateral)	1819	28
0 to 1 mo.	4	2672	6
1 to 6 mo.	1		4
6 mo. to 1 yr.	1 (unilateral)		0
1 to 5 yrs.	0	1147	6
5 to 10 yrs.	0		1
10 to 20 yrs.	0	875	7
20 to 30 yrs.	2	1759	20
30 to 40 yrs.	4	2445	28
40 to 50 yrs.	8 (1 unilateral)	2944	57
50 to 60 yrs.	6	3146	33
60 to 70 yrs.	6 (1 unilateral)	3077	6
70 to 80 yrs.	0	1780	4
80 to 90 yrs.	2	448	2
Adult (age ?)	1		
Total	44	22,112	202

doubt that the disease is always congenital and that it is the same disease in adults as in infants.

Apparently in about one-third of the cases the individuals are either born dead or die within the first month. Of those that survive over a month only a few die before the age of 20 years and the maximum death rate occurs in the fifth decade. If the disease is the same in adults as in infants, and death is due chiefly to destruction of renal tissue by cysts, why are there so few deaths between early infancy and the third decade? Why do the majority first develop symptoms after the age of 40 years? It has been suggested that in young persons the renal parenchyma between the

cysts undergoes hypertrophy to compensate for the tissue destroyed by progressive expansion of the cysts, and that in adults this compensatory hypertrophy no longer occurs. It is well known that the adult kidney does not hypertrophy as readily as that of a child. Another factor of importance is the vascular disease which develops slowly and reduces the blood supply of the parenchyma. This will be discussed more fully in subsequent paragraphs.

Sex: Large statistics indicate that there is no difference in the incidence in males and females. Braasch and Schacht had 98 females and 95 males in their group of 193 patients. In our postmortem series there were 20 males and 23 females. In the cases collected from the literature there were 96 males and 96 females.

Clinical Types: (*A*) *Surgical Type:* Often the initial symptoms are those of unilateral renal disease. There may be pain in the region of one kidney or an attack of hematuria. When the opposite kidney is not palpable an incorrect diagnosis of neoplasm may be made, and when the kidney is not notably enlarged tuberculosis and calculus must be considered. Gross hematuria occurs in about one-third of all patients (Braasch and Schacht). The pain is often caused by ureteral spasm during the passage of blood clots. Occasionally one or more cysts become infected, giving rise to pyuria and other symptoms suggestive of pyelonephritis. When the function of the two kidneys is studied separately it is sometimes found that blood and pus come only from one kidney and that it excretes little or no indigo-carmine, while the function of the opposite kidney is good. Under these circumstances it may be justifiable to remove the non-functioning kidney. A great many writers are opposed to nephrectomy, particularly because of the associated high mortality, but there are many published reports in which a long period of relief followed this operation. Blatt's patient was living 15 years after nephrectomy and the other kidney was not palpably enlarged until 12 years after the operation. Rumpel's patient was living and well 12 years after nephrectomy. The affected kidney excreted no indigo-carmine. In a case reported by Blum pain developed in the region of the left kidney at the age of 15 years. The pain continued and the patient had frequent attacks of hematuria until the age of 21 years, when the left kidney was removed because of very low function while that of the right kidney was normal. Twelve years later, at the age of 33 years, the right kidney first began to enlarge and became painful. The

patient was living at the age of 38 years, 17 years after nephrectomy. Walters and Braasch recommend nephrectomy when one kidney shows infection with a marked reduction of function. In thirty-one nephrectomies they had only one postoperative death, and 18 of their patients were living from 1 to 19 years after the operation.

Calculi are occasionally found in the polycystic kidney and may be largely responsible for the symptoms (Blatt, Cumming, Walters and Braasch, 5 cases). Rarely the cystic kidney contains a malignant neoplasm (Walters and Braasch, 3 cases), and occasionally tuberculosis is found (Uteau).

(*B*) *Medical Type:* The majority of persons with polycystic kidney disease come to the attention of internists because of symptoms referable to renal insufficiency. The clinical picture is often similar to that of chronic glomerulonephritis. The onset of uremia may be sudden but more often it develops slowly over a period of years.

Albumin is found in the urine from a trace to a large amount in the great majority of cases (180 of 190, Braasch and Schacht). This is probably due to interference with the blood supply of the glomeruli from pressure of cysts and from stretching and compression of the arteries and veins.

Gross hematuria is found in about one-third of the cases from time to time. The hematuria occurs usually in the form of attacks separated by intervals of varying length. Hemorrhage takes place into the cysts from stretching and tearing of vessels in their walls, and since frequently some of the cysts communicate with the pelvis blood escapes into the urine.

The urine is of low specific gravity and concentration tests show diminished powers of concentration. In a few instances polyuria has been reported (Götzl, Shapiro, Veil). In the terminal stages oliguria occurs frequently. The loss of ability to concentrate the urine is similar to the condition in contracted kidneys and is due to reduction of functioning parenchyma.

Edema: This is a rare symptom. Cases with edema were reported by Piersol (legs and abdomen), Shapiro (2 with edema of ankles), Atonna and Morrissey (edema of legs), Fahr (edema of feet), and Strübing and Pugh (marked generalized edema). There was a slight edema of the ankles in 5 of our cases, Nos. 39, 40, 42, 43, 44. The cause of the edema in these instances was not established, but cardiac decompensation is a possible explanation. There has apparently

been little or no study of the serum proteins, but one would not expect to find a protein depletion in the blood since there is relatively little loss of protein in the urine. The usual absence of edema indicates that cardiac decompensation plays an unimportant rôle in this disease.

Blood Pressure: Rosenberg maintains that hypertension seldom results from polycystic kidneys. In an earlier publication, before much clinical data on this point was available, I expressed a similar view based largely on the size of the heart, but since that time I have had a wider experience with this disease and a number of publications have appeared which show clearly that this view is erroneous and that hypertension is usually present in advanced stages of the disease.

In Table III all the cases are listed in which the author gave data on blood pressure or size of the heart, and in Tables IV, VI and VII our own observations are recorded. The blood pressure was recorded in 82 patients, 64 from the literature and 18 from our series. The highest blood pressure obtained is usually recorded. The highest systolic pressure was 145 mm. Hg or more in 48 cases, and was below this level in 30. In Veil's 3 cases and in 1 of ours it is merely noted as high. If we take 150 mm. Hg as the lowest level of hypertension, there are 44 at this level or above and 34 below. Of the 44 with elevated blood pressure, 22 had moderate hypertension (150 to 175 mm. Hg) and 22 had severe hypertension (175 mm. Hg or above). More than one-half of the cases (44 of 78) had a definite hypertension.

This is in agreement with the extensive study by Schacht, 1931, who found a systolic pressure of 145 mm. Hg or more in 61 per cent of 193 patients at the Mayo Clinic. The individual cases are not reported and therefore cannot be included in the table. Ritter and Baehr studied 3 cases where hypertension and uremia were present; no details were given.

Fahr suggested that the cases of polycystic renal disease without hypertension were those in which the parenchyma was not so extensively atrophied. As shown in Tables III and VII, the blood pressure was recorded in 41 cases with satisfactory clinical or anatomical evidence of rather marked renal insufficiency. In 27 of these the systolic blood pressure was 150 mm. Hg or more, while it was below this level in 14. This confirms the observation of Braasch and

TABLE III

Cases Collected from Literature Presenting Data in Polycystic Renal Disease

Author	Date	Age	Sex	Blood pressure	Renal function	Weight of heart	Weight of kidneys	Comment
		yrs.				*gm.*	*gm.*	
Kaufmann	1932	33	F	145/80	Concentration diminished			Living
Rosenberg	1932	49	F	130/ ?	?	No hypertrophy	?	
"	"	44	F	145/ ?	?	"	?	
"	"	45	F	160/ ?	?	"	?	
"	"	53	M	170/ ?	?	550	?	
"	"	55	M	?	?	Marked hypertrophy	?	
Blatt	1927	23	F	110/? (6 yrs.) 155/?	Concen. test 1010–1011	?	?	
"	"	36	F	120/?	?			Duration 10 yrs. living
"	"	43	M	130/?	?	?	?	
"	"	41	F	165/?	?	?	?	Symptoms of uremia
"	"	?	M	135/?	Concen. test 1000 to 1017	?	?	
Halbertsma ...	1931	10	F	150/110	Concen. test 1010–1019, PSP 35			Living
"	"	40	M	210/170	Urea N 179, PSP 9			Duration 16 yrs.
Götzl	1933	54	M	200/130 170/110	NPN 155, 220	?	Very large	
Fuller	1929	74	M	190/120	Urea 90		Large	Living
"	"	45	M	150/?	Urea 20.8		Large	Living
"	"	43	F	150/115	Urea 39		Large	Living
"	"	42	M	145/100	Urea 45		Large	Living
"	"	40	M	185/120	Urea 40		Large left	Living, 7 yrs. duration
"	"	16	F	100/?	Concen. good		Enlarged	Living
"	"	18	M	105/80	Urea 13.6, concen. good		Palpable	Living

NPN = non-protein nitrogen. Urea N = urea nitrogen, mg. per 100 cc. of blood. PSP = phenolsulphonephthalein, per cent in 2 hours.

NPN = non-protein nitrogen. Urea N = Urea nitrogen.

Podgurski	1930	41	M	120/95	?	Enlarged	Very large	
"	"	52	M	160/105 195/100	Urea 141, 203	550	Very large	
"	"	74	F	180/105 145/95	Urea 53, NPN 56	Marked hypertrophy	Three times normal	
"	"	48	M	150/90	Concen. test 1008–1024	Hypertrophy	Very large	
"	"	48	F	140/105 (3 yrs.) 135/70	Concen. test 1001–1010 Urea 68 (3 yrs.), 374 (recent)	Hypertrophy	2000	
"	"	43	M	180/75	Concen. test 1008–1010	Marked hypertrophy	Very large	
Fahr	1929	45	M	215/? 145/?	NPN 126	360	2200	
"	"	61	M	?	?	380	Large	
"	"	46	M	161/?	?	440	Left 950	
"	"	45	M	140/?	NPN 348	520	520	Uremia
"	"	55	M	210/?	?	555	Large	
"	"	85	F	145/?	NPN 146	Not enlarged	?	
Piersol	1928	42	M	130/60	Concen. test 1006–1010	Moderate hypertrophy	4420	
"	"	64	M	218/165	Urea N 160, creatinin 21	?	1985	
Washburn	1930	47	F	140/90 (1 mo.)	Urea 23.8 (14 mo.)	?	1575	
Shapiro	1929	55	F	138/74 (6 yrs.)	?	?	?	
"	"	29	M	180/? (3 yrs.) 160/? (2 mo.)	?	?	?	
"	"	36	F	186/? (1 yr.)	?	?	?	
"	"	10	M	134/80	NPN 42, urea 21			Living
"	"	42	M	140/82	NPN 78, urea 38			Living
"	"	46	M	126/82 140/90	NPN 69 to 342, creatinin 10.3	?	?	
"	"	48	M	190/120 220/?	NPN 34.2, urea 19.6			Living

TABLE III (*Continued*)

Cases Collected from Literature Presenting Data in Polycystic Renal Disease

Author	Date	Age	Sex	Blood pressure	Renal function	Weight of heart	Weight of kidneys	Comment
		yrs.				*gm.*	*gm.*	
Shapiro	1929	37	M	162/110	NPN 375, urea 250	?	Left 5220	
"	"	52	M	164/96	NPN 160, urea 54, creatinin 10.4	?	2717	
"	"	28	F	130/90	Urea 32, PSP 60			Living
"	"	42	F	122/84 (7 yrs.)	?			Living
Gottlieb	1925	28	F	120/75	Sp. gr. 1000 to 1018			Living
Litzner	1929	40	M	140/? 150/?	Urea 354, concen. test 1004–1010	?	Large	
Ludowigs	1926	46	M	135/?	Delayed excretion of indigo-carmine			Living
Grauhan	1926	43	M	105/75	?	?	?	
"	"	46	M	170/120	Concen. test 1003–1017, NPN 63			Living
"	"	42	F	160/?	Concen. test 1001–1020, NPN 61			Living
"	"	40	F	120/70	Concen. test 1001–1011, NPN 43			Living
"	"	36	M	240/?	Concen. test 1006–1011, NPN 112			Living
"	1926	44	F	106/55	NPN 189			Living
Veil	1914	52	F	Elevated	?	?	?	
"	"	42	F	"	No retention of nitrogen	?	?	
"	"	46	F	"	PSP 50 in 4 hrs.	?	?	
Greene	1922	3.5	F	108/70 100/65	PSP 7, NPN 48	50	17	
Cumming	1928	31	M	168/132	PSP 65	?	?	
"	"	36	M	140/90	NPN 172			
Katz and Mühe	1924	35	M	153/126	NPN 97 to 60			Living
"	"	45	F	155/100	NPN 34, concen. test 1009–1011	Slight hypertrophy		Death from intracranial hemorrhage
McKinlay	1920	30	M	230/130	?	400	Very large	

Schacht that there is a somewhat higher incidence of hypertension in the more advanced stages of the disease. Several authors in studying individual cases over a period of years have noted a gradual rise of blood pressure.

It may be concluded that a systolic pressure of 150 mm. Hg or higher is found in over half of adults with clinical symptoms, and that the percentage with hypertension is still higher in the group with marked renal insufficiency. However, cases occur in which no hypertension develops. The basis of the hypertension will be discussed in a subsequent paragraph.

Hypertrophy of the Heart: In the literature we have found the weight of the heart recorded in only 8 adults, the average weight being about 470 gm. In 7 cases the heart was described as hypertrophied, and in 4 as not enlarged, no weights being given.

The weight of the hearts in our series is shown in Tables VI and VII. In the subclinical group (Table VI) no heart weighs over 400 gm., and 4 of them weigh less than 325 gm. In the clinical group (Table VII) the weights are as follows: 250 to 350 gm. 7 hearts, 350 to 450 gm. 5 hearts, over 450 gm. 6 hearts. In the clinical group the hearts are definitely larger. It may be concluded that cardiac hypertrophy occurs frequently in polycystic renal disease but that it is not as prominent a feature as one would expect in view of the frequency of hypertension. Perhaps the blood pressure is not so high over a long period of time as in primary hypertension.

Renal Insufficiency: The majority of the symptoms in polycystic renal diseases are due to renal insufficiency. The clinical phenomenons in the usual case are such as are found with contracted kidneys. There may be gastro-intestinal symptoms, such as loss of appetite, nausea, vomiting, constipation or diarrhea. Anemia and weakness are common symptoms, and there may be a marked loss of weight. Periods of malaise and headache occur. A definite impairment of renal function is demonstrable in about two-thirds of the patients when they first consult a physician. The functional disturbances are similar to those found in patients with contracted kidneys. There is a decreased elimination of phenolsulphonephthalein, a retention of nitrogenous substances in the blood and a decrease of the ability to concentrate the urine. These tests indicate a decrease of functioning parenchyma in the kidneys. Death is usually due primarily to renal insufficiency, unless one of the kidneys becomes infected.

Cerebral Hemorrhage: Sieber, in his survey of the literature in 1901, found that 10 of 212 patients died of cerebral hemorrhage. Dunger reported the death of a woman, aged 54 years, from a ruptured aneurysm in the corpus callosum. Her daughter died at the age of 26 years from a pontine hemorrhage. Blatt noted death from cerebral hemorrhage in a woman 46 years old. Katz and Mühe found a ruptured aneurysm of the anterior communicating artery in a woman 45 years old, and McKinlay described an intracranial hemorrhage in a male 30 years of age. One of our cases, a male 40 years of age, suffered a hemiplegia at the age of 37 years but died of uremia. The incidence of cerebral hemorrhage is low and it is possible that it is due to an associated arteriosclerosis or primary hypertension independent of the renal disease. The rise of blood pressure caused by cystic kidneys would, however, tend to cause rupture of arteriosclerotic vessels in the brain.

Duration of Symptoms: Braasch and Schacht found that 45 per cent of 193 patients lived less than 4 years after the onset of symptoms. Twenty-five lived more than 10 years, and 9 more than 20 years. Cases of long duration are reported by several authors: Blatt (8 yrs., 10 yrs., 10 yrs., 18 yrs.), Halbertsma (16 yrs.), Wulff (15 to 20 yrs.), Collinson (11 yrs.), Götzl (16 yrs.), Fuller (12 yrs.), Blum (23 yrs.), Atonna and Morrissey (12 yrs.), Niecke (11 yrs.), Cumming (8 yrs., 9 yrs., 16 yrs.).

Retinal Changes: Braasch and Schacht found the fundi negative in 43 per cent, retinal sclerosis without retinitis in 31 per cent, and retinitis with retinal sclerosis in 20 per cent of their patients. There are apparently no other studies of the eyegrounds in the literature dealing with polycystic renal disease, but in the literature of hypertension there are occasional descriptions of a retinitis in this form of renal disease. It is believed that the retinitis results from high blood pressure, since it resembles the retinal changes seen in other forms of hypertension.

Effects of Pregnancy: Pregnancy increases the work of the kidneys and not only intensifies any preëxistent symptoms but may also bring out symptoms in a compensated or latent stage of the disease. Blatt described a patient, 36 years of age, who first developed symptoms during pregnancy. There was marked edema, albuminuria and vomiting. The child was born at 8 months, and for 1 year afterwards there was a general weakness, albuminuria and headache.

The patient then remained well for 5 years, after which the symptoms reappeared. A patient reported by Heinsius developed marked edema, heavy albuminuria, visual disturbances and severe dyspnea during the seventh month of pregnancy. At postmortem abscesses were found in the large cystic kidneys and the liver also was cystic.

Symptoms apparently do not develop during pregnancy unless the renal reserve is low. In Podgurski's case the patient went through thirteen pregnancies and first developed renal symptoms at the age of 73 years. There are many cases of this type in the literature.

The unfavorable effects of pregnancy are the same as those occurring in chronic glomerulonephritis and are due to the same cause, *viz.* a marked decrease of renal parenchyma. Pregnancy puts an additional load upon the kidneys and when the renal reserve is low symptoms of renal insufficiency develop.

Influence of Heredity: It has been known for many years that inheritance plays a rôle in polycystic renal disease. Families with a high incidence of the disease have been reported by Dunger, Paus, Cairns, Fuller and Shapiro. Dunger, 1904, found the disease in 5 children of the same mother. In addition he observed the disease in a mother 54 years old, and in her daughter aged 26 years. Paus, 1914, in the family which he studied found 4 members in the first generation, 2 of whom had cystic kidneys. One of those with cystic kidneys had 14 children, of whom 4 had cystic kidneys; the other with cystic kidneys had 3 children, none with the disease. One of the normal members of the first generation had 4 normal children but a granddaughter had cystic kidneys. Cairns, 1925, noted 10 cases in three generations of a family. Fuller, 1929, described 9 cases in 27 members of a family in four generations. Shapiro, 1929, found the disease in a mother, in 4 of her children, and in 1 of her grandchildren.

In addition to these larger groups a great many writers have called attention to more than 1 case in a family. Beck, 1901, reported 3 sisters with polycystic renal disease. Bunting, 1906, found the disease in 2 newborn children of the same mother. Wobus, 1918, found 4 children of the same mother with polycystic kidneys. Rumpel, 1921, found two families each with 3 cases of cystic kidneys in two generations. Cumming, 1928, found a familial history of the disease in 11 of 31 cases which he studied. Halbertsma, 1931, found

the disease in a man 40 years old and his daughter 10 years of age. Balogh, 1933, reported 3 cases in the first generation of a family and 3 in the second. A great many observations similar to those mentioned above have been published. Maier, 1924, quoted twenty-four writers who had found examples of hereditary polycystic kidney disease, and Bunting also gives a number of references. It is clearly established that heredity plays a remarkable rôle in polycystic renal disease. The disease may be transmitted by either sex and it is probably a dominant character. It is not known whether apparently normal persons who transmit the disease to their offspring have normal kidneys or a latent form of cystic disease.

Renal Rickets: Like other forms of chronic renal disease polycystic kidneys in children may lead to dwarfism or rickets. Greene, 1922, described a severe case of rickets in a girl 3½ years of age. The child was underdeveloped and underweight and had a marked renal insufficiency. The cystic kidneys were small, 10 gm. and 7 gm.

It is probable, however, that Greene's case was not true congenital cystic renal disease, but hypertrophy and cystic dilation of tubules secondary to some form of atrophy or hypoplasia. This topic is discussed more fully in a subsequent paragraph. Mazzeo, 1930, described a rachitic dwarf 10 years of age with renal insufficiency due to cystic kidneys. The height was 88 cm.

Diagnosis: Braasch and Schacht in 193 patients found bilateral palpable kidneys in 151, enlargement of one kidney only in 30, and no enlargement in 12. When both kidneys are enlarged there is usually little difficulty in establishing the diagnosis. There may be local pain or tenderness in one or both kidneys or symptoms due to pressure on the intestines or other structures, but for the most part the symptoms are referable to renal insufficiency and do not differ essentially from those associated with chronic glomerulonephritis. A moderate edema of the lower extremities is occasionally seen, but marked edema is very unusual. Cardiac decompensation seems to be uncommon. The attacks of hematuria are peculiar to this disease.

The cases in which only one kidney is enlarged present some diagnostic difficulties and have been confused frequently with renal tumor or hydronephrosis. When a calculus is demonstrated, as happens occasionally, the nature of the underlying disease is even more difficult to recognize. It is not unusual to find a marked difference in the size of the two kidneys even when both are enlarged. They

may also exhibit striking differences in function. When the disease is demonstrable in only one kidney, it by no means follows that it is not bilateral. In a case reported by Blum the right kidney first showed a demonstrable enlargement 12 years after the left had been removed. In a unilateral enlargement an accurate pyelogram usually leads to the correct diagnosis. Since Adrian and von Lichtenberg pointed out the characteristic shape of the pelvis, as revealed by the pyelogram, the accuracy of the clinical diagnosis has improved markedly. The most convincing pictures are obtained on large kidneys, the typical appearance being elongation of the pelvis and calyces. The calyces may be widened, especially at their tips, or one or more calyces may be flattened or obliterated. The lengthening of the pelvis and calyces is due to the increased size of the kidneys and their distortion is due to the encroachment of cysts upon them. In small kidneys the diagnosis may be uncertain.

When neither kidney is enlarged, as in our Case 43, a diagnosis of chronic glomerulonephritis or hypertensive kidney is usually made and the true nature of the disease is not recognized. In our case there was hypertension, cardiac hypertrophy and renal insufficiency, and no symptom or sign suggesting cystic kidneys. Possibly a pyelogram would have given the correct interpretation.

Pathology

Polycystic kidneys retain the shape of a normal kidney, the various dimensions being increased proportionally. There may be some displacement caudally because of the increased weight. When very large they fill the lateral retroperitoneal areas, displacing the intestines anteriorly and medially.

The external surfaces are closely set with rounded elevated areas corresponding to the underlying spherical cysts. On section a honeycomb appearance is noted. In advanced cases the cysts are separated only by narrow bands of tissue, and little or no normal parenchyma is to be seen (Fig. 1). Occasionally, even in advanced cases, small islands of parenchyma 1 cm. or more in diameter are found, and in cases in which death is not due to renal insufficiency there may be a large amount of normal parenchyma between the cysts (Fig. 2). When the parenchyma is reduced to a minimum the persistent portions are usually in the subcapsular zone. Usually

both cortex and medulla are filled with cysts and no distinction between these portions can be made, but in rare instances there are no cysts in the medulla (Herxheimer, Case 1). Schaefer described a kidney with a row of cysts at the cortico-medullary junction and none elsewhere. One pole of the kidney may be filled with cysts and the other pole normal (Cases 4 and 20). In the smaller kidneys the cysts may all be small and of uniform size, giving a spongy texture to the tissue; in the usual case, however, there is a rather marked variation in size, an occasional cyst approaching the dimensions of a large solitary cyst. In general there is a direct relation between the size of the kidney and the size of its cysts, and one gets the impres-

TABLE IV

Unilateral Polycystic Kidneys

Case No.	Autopsy No.	Age	Sex	Blood pressure	Weight of heart	Weight of kidneys	
						Right	Left
		yrs.			*gm.*	*gm.*	*gm.*
1	20–260	6 mo.	M	?		73	8.5
2	28–1732	45	F	?	325	500	210
3	30–1811	Sb	F			10	33
4	34–987	65	F	195/110	499	177	666

sion that enlargement of a cystic kidney is due to increase in the size of the cysts rather than to an increase in their number.

Frequently some of the cysts communicate with the calyces. When hematuria occurs it is commonly due to bleeding within a cyst that communicates with the pelvis. These communicating cysts may represent primary outgrowths from the pelvis or their connections may have been established secondarily. The cysts are filled with a watery fluid which is usually clear but sometimes colored brown, black or red from admixture of old or fresh hemorrhage (Davis). Chemical examination reveals a high content of urea, uric acid and creatinin. In Piersol's patient the fluid from the cysts contained: uric acid 20 mg., creatinin 28 mg., and urea nitrogen 300 mg. per 100 cc. Litzner found: urea 321.8 mg., and uric acid 12.6 mg. per 100 cc. In both of these cases there was a marked retention of nitrogen in the blood corresponding roughly to the content of the cystic fluid. Singer and Brams found 45.9 mg. of urea per

100 cc. in the cystic fluid of a newborn infant. Strübing found serum albumin and serum globulin as well as urea in cystic fluid. The

TABLE V

Bilateral Polycystic Kidneys in the Newborn

Case No.	Autopsy No.	Age	Sex	Crown-heel length	Cystic liver	Weight of heart	Weight of kidneys	Arteries	Comment
				cm.		*gm.*	*gm.*		
5	18–258	14 wks.	F	56	–	?	60 65	?	Congenital syphilis
6	20–243	11 da.	F	50	–	?	100 65	Normal	No edema, no note on the urine
7	21–33	30 min.	M	49	–	35	155 160	?	Bilateral hydrocele
8	24–207	Sb	M	47	–	29	67 69	?	
9	26–880	Sb	M	?	+ many cysts	18.4	407 567	Normal	Meningocele, anomaly of tongue
10	27–663	5 da.	M	44	–	20	122 114	Normal	Clinical uremia
11	27–1184	Sb	M	44	–	16	259 275	Normal	Club foot, undescended right testis
12	30–257	Sb	F	37	–	18	300 275	Normal	Encephalocele, club foot, supernumerary toe
13	33–169	17 da.	M	52	–	?	Large	Medial fibrosis	Oliguria. Albumin, pus and blood in the urine
14	34–1703	Sb	?	?	–	?	20 20	Normal	
15	26–983	Sb	F	39	–	?	21 25	?	Anencephaly, craniorachischisis
16	31–1201	Sb	M	32	–	?	24 21.5	?	Filled with small cysts

Sb = stillbirth.

presence of a high urea content in cystic fluid is to be attributed to diffusion from the blood plasma and not to secretion of urine: pericardial fluid also has a high urea content in renal insufficiency. There

are apparently no observations on the urea content of cystic fluid from cases without renal insufficiency.

The unilateral cystic kidneys (Table IV) will be discussed under the newborn and the adult groups.

Cystic Kidneys in the Newborn

In the group of newborn infants there is an enormous variation in the size of the kidneys. In the 12 cases in our series the combined weight of the kidneys varied from 40 gm. to 974 gm. (Table V). The larger kidneys usually have larger cysts but not a greater number than are found in the smaller kidneys. The destruction of parenchyma is often as extensive in small kidneys as in large ones. In estimating the extent of the renal enlargement the crown-heel length of the infant should be considered, since many of them are premature and the relative increase in size of the kidneys is therefore greater than the weight indicates.

The markedly hypoplastic cystic kidneys have not been included in this study since their pathogenesis may be different.

On section the cortex seldom can be distinguished from the medulla and all parts of the organ are filled with cysts. Often there is a defective development of the pelvis and calyces, and some writers have stressed aplasia of the medulla (Staemmler).

Our cases of bilateral polycystic kidneys in the newborn are listed in Table V. A more detailed description will now be given of the 7 cases in which material was available for microscopic study.

CASE 6. On gross examination numerous very small cysts were found which gave a spongy texture to the parenchyma.

Microscopically most of the glomeruli and tubules are found in small groups in the subcapsular zone, but a few are scattered between the cysts. The medulla is composed of large cysts separated by dense connective tissue; there are no collecting tubules. An abundant, rather dense connective tissue is found in the deep part of the cortex. Some of the normal tubules in the subcapsular zone open into the smaller peripheral cysts. A great many cysts in the cortex, and some of those in the medulla contain a glomerulus projecting into the cavity.

CASE 9. Microscopically there are small islands of normal parenchyma in the subcapsular zone. Nearly all of the kidney is composed

of cysts separated by an enormous amount of loose connective tissue. Very few collecting tubules are found. There are a few tubules and glomeruli in the connective tissue between the cysts. Many small cysts in the subcapsular zone contain a glomerulus projecting into the cavity, and a few of these cysts may be traced into dilated tortuous tubules.

CASE 10. On gross examination the kidney showed a spongy texture and no large cysts were visible.

Microscopically the cortex is composed of long, dilated, tortuous tubules connected with glomeruli in the subcapsular zone. Between the dilated tubules are many atrophic glomeruli with a short segment of tubule or without a tubule. There is a great decrease in glomeruli. The medulla is very fibrous and filled with cystic structures. There is no fibrosis of the cortex.

CASE 11. Microscopically the superficial zone of the cortex is intact. In the deeper part of the cortex the tubules become dilated and some of them open into fairly large cysts. The medulla is composed of very large cysts separated by an abundant, loose, areolar tissue which extends into the deeper part of the cortex. There are only a few collecting tubules. None of the cysts contains a glomerulus.

CASE 12. Microscopically there is a thin subcapsular zone of glomeruli and underdeveloped tubules. Cysts fill the medulla and the cortex up to the subcapsular zone. There is a marked reduction in the number of glomeruli. The medulla is composed of dense fibrous tissue suggesting the medullary fibromas found in adults. There are no collecting tubules. Normal tubules may be traced into small cysts which seem to be dilated segments of the tubule.

CASE 13. On microscopic examination no normal areas of parenchyma are found. There are cysts of varying size and duct-like structures separated by dense fibrous tissues. Occasionally a glomerulus with a short tubule is seen. The walls of the arteries and arterioles are thicker than normal. They show a marked medial fibrosis but no intimal thickening. There is no narrowing of their lumens.

CASE 14. The ureter, pelves and calyces are present. The pyramids are not distinct. Cysts are found throughout the cortex and medulla. There are only a few small nests of glomeruli and tubules

between the cysts. The cysts are separated by a fairly dense connective tissue. A few cysts contain glomeruli. The arteries curve around the larger cysts.

CASE 1. The unilateral cystic kidney of an infant 6 months old (Table IV) may be considered with this group. It presented a structure similar to the preceding cases but the parenchyma was not so extensively destroyed. On section a few small islands of fairly normal parenchyma were seen. There was a small ureter but no pelvis or calyces could be found. The cysts were closely set and some reached a diameter of 4 cm.

Microscopically the small islands of cortex are composed of normal tubules and glomeruli. Many of the cysts are tubular structures with a fibromuscular wall which Busse considered evidence of their origin from the pelvis. There are occasional rudimentary tubules between the cysts. The interstitial tissue is abundant and dense, especially in the medulla. No collecting tubules are seen.

Comment

One of the most prominent microscopic features is an enormous increase of interstitial connective tissue. All of the authors comment on this peculiarity, although a few state that it is not always conspicuous. It varies from a loose areolar to a dense fibrous structure and is usually more abundant and dense in the medulla than in the cortex. The superficial part of the cortex under the capsule is often free from this connective tissue increase and it is in this region that islands of fairly normal parenchyma may be found. In the medulla the connective tissue replaces nearly all of the collecting tubules and it may show dense rounded masses that closely resemble the medullary fibromas so often seen in normal kidneys of adults. It is highly probable that medullary fibromas are derived from an excess of embryonic connective tissue. It is unlikely that the excess of connective tissue is the fundamental disturbance since occasionally there is no great amount present, but it is an important factor in the subsequent pathogenesis of the disorder. It tends to become more dense and fibrous as the individual grows older, it compresses tubules and glomeruli and is one of the important factors that bring on progressive renal insufficiency.

Occasionally areas of cartilage or smooth muscle are found in the interstitial tissues (Busse, Berner). The significance of the excess of connective tissue is unknown. Possibly it is a compensatory result of the hypoplasia of the tubules.

Another conspicuous feature of the congenital cystic kidney of the newborn is the marked reduction in the number of nephrons. A great many contributors have noted this. It has been estimated that the number may be reduced to 10 per cent of the normal, but no actual counts have been made. In the medulla there are usually only a few collecting tubules. In our cases, Nos. 6, 10, and 12, no normal collecting tubules were found in the sections studied, and there were only a few in the others. Normal convoluted tubules and glomeruli are commonly found only in small islands usually in the subcapsular zone. Sometimes there are only rudimentary tubules and glomeruli between the cysts and no areas of normal cortex (Case 13). Wakely found no tubules or glomeruli in 1 case. Normally the collecting tubules form by repeated dichotomous branching of the primitive outgrowths of the pelvis, and it is evident that this process is disturbed so that only a few collecting tubules are formed, or they become detached from the main branch after their formation. Some of the cysts may represent dilated outgrowths from the pelvis, especially those with a fibromuscular wall.

The cysts are lined with a single layer of epithelium which is usually cubical but sometimes columnar, or it may be flattened so that it resembles endothelium. The cytoplasm is commonly clear and the cell boundaries may be distinct but sometimes there is a granular cytoplasm. Often the lining epithelium has proliferated to form papillary ingrowths, and it is this feature that suggested the neoplastic theory of the cystic kidney.

In some kidneys numerous cysts show a glomerulus projecting into the lumen, the glomerulus being supplied with afferent and efferent arterioles and having a normal structure. Such cysts have been interpreted as dilated capsular spaces. In other kidneys none of the cysts is supplied with a glomerulus. Beckmann, 1856, described glomerular cysts. Frequently one sees a normal glomerulus connected with a normal tubule which opens into a cyst. Apparently some of the cysts represent dilated segments of a tubule. There is abundant evidence that some cysts communicate with capsular spaces and tubules but apparently they seldom drain into the pelvis.

Von Mutach, 1895, studied a number of small cysts, 0.5 to 2 mm. in diameter, in serial sections and was able to show that each was a dilated segment of a tubule.

Hyaline glomeruli are almost invariably present in adult polycystic kidneys, but they are evidently rare in infants. There were none in our cases. Staemmler, however, noted a number of hyaline glomeruli in a stillborn infant.

The arteries and arterioles show a normal structure in all of our cases except one (Case 13), in which a definite medial fibrosis is present. This caused the media to appear somewhat thicker than normal and more homogeneous. There is no change in the intima and no narrowing of the lumen in any instance. Staemmler mentioned a thickening of the walls of the arteries in a stillborn infant which also had many hyaline glomeruli. I have found no other reference to arterial disease in the polycystic kidneys of infants.

Renal insufficiency in the newborn group is clearly due to hypoplasia of the parenchyma. There is a great reduction in the number of nephrons and the majority of those present apparently do not communicate with the pelvis. It is evident that those who survive into adult life must have originally had more normal parenchyma than is present in this group. Renal insufficiency is readily demonstrable by functional tests (Tow).

We shall now direct attention to the group of patients with cystic kidneys in which death was due to some extrarenal cause and no symptoms referable to the kidneys were present (Table VI).

Cystic Kidneys in the Adult

Case 17. On gross examination the external surfaces of the kidneys were finely granular and the cortices were somewhat thinner than normal. There were numerous small cysts from 1 to 6 mm. in diameter scattered over the surfaces and throughout the cortical portions. There was an abundance of normal parenchyma.

Microscopically the cysts are lined by cubical epithelium and show no fibrosis or atrophy about them. There is no evidence that they are compressing the kidney by expansion. There is no indication that the disease would have progressed toward renal insufficiency.

Case 18. The patient was troubled for a number of years with

weakness, edema of the ankles and dyspnea on exertion. There was a trace of albumin in the urine. These symptoms were attributed to the very large cystic liver found at postmortem. On section numerous cysts were found scattered throughout both cortical and medullary portions. There was abundant normal parenchyma.

Microscopically the cysts are lined by cubical or flattened epithelium. Some of the larger ones are surrounded by a zone of fibrous

TABLE VI

Polycystic Kidneys with No Symptoms Referable to the Kidneys (Subclinical Group)

Case No.	Autopsy No.	Age	Sex	Blood pressure	Cystic liver	Weight of heart	Weight of kidneys	Intimal thickening		Interstitial tissue	Cause of death
								Arteries	Arterioles		
		yrs.				*gm.*	*gm.*				
17	23–152	85	F	120/?	–	270	110 90	2	0	–	Lobar pneumonia
18	23–756	61	F	124/73	+++ 2430 gm.	300	350 400	2	0	–	Lobar pneumonia
19	25–481	52	M	?	+	400	Twice normal	2	2	–	Cerebral hemorrhage
20	26–9	35	F	?	+	375	325 525	1	0	–	Subarachnoid hemorrhage
21	26–591	65	M	?	–	320	380 500	2	0	–	Perforated ulcer
22	27–272	52	F	?	++	235	260 190	2	0	–	Lobar pneumonia
23	29–537	33	F	172/102	–	380	500 350	2	1 –	–	Subarachnoid hemorrhage

tissue. There is atrophy of the parenchyma in narrow septa between the cysts, but none elsewhere and there is very little evidence of a progressive destruction of the parenchyma. That this is a true congenital cystic kidney is indicated by the cystic liver and the presence of cysts in the medulla. There is no increase of interstitial tissue. This case may be interpreted either as an early stage of clinical cystic kidney disease or as a moderate degree of cystic disease which would not have progressed to renal insufficiency. The latter interpretation seems more probable.

CASE 19. Sudden death. No previous illness known. On section the kidneys were filled with cysts of varying size. Both cortex and

medulla were involved. There was a large amount of normal parenchyma.

Microscopically the smaller cysts are surrounded by normal parenchyma. The larger cysts are usually surrounded by a zone of fibrous tissue, and the narrow septa between them are composed of fibrous tissue. There is some displacement of collecting tubules by the medullary cysts. On the whole there is evidence of a slow increase in size of the cysts. The arteries and arterioles show the intimal thickening characteristic of hypertension.

CASE 20. No symptoms of renal disease. The larger kidney was filled with cysts of varying size which occupied both cortex and medulla. There was a large amount of normal parenchyma. Only one pole of the smaller kidney was cystic.

Microscopically there is very little evidence of atrophy of the parenchyma except in thin septa between the cysts. The arteries are practically normal.

CASE 21. No symptoms except those referable to duodenal ulcer. On section numerous cysts of different sizes were scattered throughout the cortex and medulla. There was a large amount of normal parenchyma.

Microscopically the thin septa between the cysts are composed of atrophic parenchyma, and there are wide zones of pressure atrophy around some of the larger cysts. There is, therefore, definite evidence that the larger cysts are expanding. Some of the large cysts are lined by flattened epithelium. There is no atrophy about the small cysts. The arteries show only the intimal thickening corresponding to the age.

CASE 22. Admitted in shock. No history of kidney disease. Both kidneys contained numerous cysts in both cortical and medullary portions. There was, however, a large amount of normal parenchyma. A calculus was found in an upper calyx of the left kidney.

Microscopically there is complete atrophy of the parenchyma in the narrow septa between the cysts and external to large cysts which lie near the surface. The pressure atrophy about the large cysts indicates a slow increase in size. There is no change in the tissue surrounding small cysts. The arteries show the typical senile intimal thickening and there are a few, small, wedge-shaped areas of atrophy at the surface, due to arterial disease.

CASE 23. Some albumin in the urine. Hemorrhages in the fundi. Urea nitrogen 14 mg. per 100 cc. of blood. Virilism. Adenoma of the right adrenal 2 cm. in diameter. On section there were a number of cysts from 5 mm. to 3 cm. in diameter scattered throughout the cortex and medulla. The cysts were not very numerous and there was abundant normal parenchyma between them.

Microscopically there is a little pressure atrophy about the larger cysts. The arteries and arterioles show the intimal thickening characteristic of hypertension. In arteries that curve about large cysts a definite medial fibrosis is noted. A few small atrophic areas have resulted from the arteriolosclerosis.

The patients with symptoms referable to the kidneys are listed in Table VII. Supplementary data on each case is given in the following paragraphs.

CASE 24. The patient had noticed a mass in the left side for several years, but it was not painful. She had had two pregnancies and during each there was a marked edema of the ankles. Palpable left kidney. No indigo-carmine from either kidney in 20 minutes. Symptoms and death from bacterial endocarditis. On section each kidney was filled with closely-packed cysts from 2 mm. to 5 mm. in diameter. The largest cyst was 8.5 cm. in diameter. There were large areas of normal parenchyma scattered between the cysts (Fig. 2). Both cortex and medulla were cystic.

Microscopically the islands of solid tissue show a fairly normal structure. There is more or less complete atrophy of parenchyma in the septa between the cysts and there is a zone of pressure atrophy around the larger cysts. The arteries in the walls of large cysts show medial fibrosis with some thickening of the media but no intimal change. The atrophy is clearly due to expansion of cysts and not to arterial disease. The large expanding cysts are usually lined by a flattened epithelium.

CASE 25. Frequent burning urination, pyuria for 4 months. Left kidney palpable. Small amount of albumin in the urine. Blood urea nitrogen 18.6 mg. per 100 cc. 2 weeks before death. Pus from right ureter. At postmortem extensive suppuration was found in the larger left kidney. Both kidneys were filled with cysts separated by thin septa or islands of parenchyma.

Microscopically the islands show a fairly normal cortex except for

TABLE VII

Polycystic Renal Disease (Clinical Group)

Case No.	Autopsy No.	Age	Sex	Blood pressure	Functional tests	Cystic liver	Weight of heart	Weight of kidneys	Arteries		Arterioles		Cause of death
									Intimal thickening	Medial fibrosis	Intimal thickening	Medial fibrosis	
		yrs.					*gm.*	*gm.*					
24	27–506	27	F	78/52	No indigo-carmine in 20 min.	–	240	820 861	1	2	0	0	Bacterial endocarditis
25	30–456	66	F	180/90	PSP 30%, Urea N 18.6 mg.	–	320	500 260	3	1	2	0	Pyelonephritis
26	30–1790	Adult	M	?	?	+	480	450 450	2	1	0	0	Postoperative shock
27	14–139	44	F	?	?	+	?	600 450	3	0	0	2	Postoperative infection
28	15–381	52	M	?	?	–	480	590 700	2	2	0	2	Fracture of skull
29	14–63	33	F	?	?	+++ 9510 gm.	350	550 600	?	?	?	?	Postoperative shock
30	32–146	64	F	210/190	?	–	285	330 275	3	2	0 2	2	Uremia
31	25–297	45	F	90/50	Sp. gr. 1010	–	292	842 663	1	1	0	0	Uremia
32	26–599	59	M	124/84	?	++	250	Very large	?	?	?	?	Uremia

33	28–1109	48	M	?	Urea N 118 mg.	–	355	520 545	1	2	1	1	Uremia
34	29–1159	25	M	165/110	PSP 0, Urea N 174 mg.	–	420	840 1240	1	1	0	1	Uremia
35	34–623	48	M	144/84	NPN 163. 7 mg.	–	550	1400 960	?	?	?	?	Uremia
36	16–310	42	F	?	?	–	?	1250 1280	3	1	0	3	Uremia
37	23–92	39	F	?	?	–	?	1300 2500	1	2	0	3	Uremia
38	31–1150	58	F	235/110	?	–	420	1100 1570	?	?	?	?	Uremia
39	31–2054	68	F	248/140	Urea N 142.9 mg.	–	325	1450 2150	?	?	?	?	Uremia
40	33–298	40	M	190/134	Urea N 109.9 mg.	–	560	2000 1800	3	1	0	1	Uremia
41	33–1540	40	M	High	?	–	430	1875 2580	0	3	0	3	Uremia
42	34–841	57	F	170/110	Urea N 234 mg.	++	275	550 900	3	0	0 to 1	0	Uremia
43	31–1682	72	M	165/85	Urea N 138.3 mg.	–	780	220 180	3	2	1 to 3	1	Uremia
44	34–1701	88	M	206/118	Urea N 85.4 mg.	–	536	90 99	3	2	3	1	Uremia

PSP = phenolsulphonephthalein (output in 2 hrs.). NPN = non-protein nitrogen. Urea N = urea nitrogen. The numerals 1, 2, 3 show the degree of the indicated process.

leukocytic infiltration. The arteries show the hypertensive form of intimal thickening.

CASE 26. Nephrectomy for hematuria. Postoperative death. On section cysts were found throughout the kidneys, leaving only small islands of parenchyma between them.

Microscopically there is atrophy of the parenchyma between and around the larger cysts. There are small areas of subcapsular atrophy related to cysts near the surface. The arteries show a moderate amount of intimal thickening.

CASE 27. The patient had noticed a mass in the right side of the abdomen about 2 years before her death. There were attacks of painful hematuria on several occasions. The right kidney was removed. Death about 6 weeks later from infection of the surgical wound. On section the entire kidney was a mass of cysts but there were some fairly large islands of solid parenchyma.

Microscopic examination shows pressure atrophy of the parenchyma between and around the larger cysts. There are also atrophic tubules with hyaline glomeruli scattered through the solid islands of parenchyma. The large and small arteries show an extreme intimal thickening (Fig. 3) and the arterioles show a marked medial fibrosis with no intimal disease. The medial fibrosis causes the walls of the arterioles to appear thick and homogeneous. The arterial disease is apparently responsible for the hyaline glomeruli and is therefore contributing to the renal insufficiency, but the cysts are the chief cause of the parenchymal atrophy.

CASE 28. The patient died shortly after sustaining a fracture of the skull. Although no clinical data were available, the extensive destruction of the kidneys justifies the classification of this case with the clinical group. On section the kidneys were filled with cysts but there were a number of areas of solid tissue, 1 to 2 cm. in diameter, in a longitudinal section. Both cortex and medulla were cystic.

Microscopic sections show extreme atrophy of the parenchyma in the narrow septa between the cysts and around the large cysts. The solid areas show many normal tubules and glomeruli. The majority of the glomeruli show some thickening of the capillary basement membranes, and in many of them there are large hyaline areas due to fusion of the thickened membranes. Some glomeruli

are completely hyalinized. Both arteries and arterioles show medial fibrosis. The size of the heart indicated that hypertension was present, and this may be responsible for the thick glomerular capillary walls. The chief cause of the destruction of the kidney is expansion of cysts, but a contributory cause is a slow hyalinization of the glomeruli.

CASE 29. Enlargement of abdomen for 3 years. Urine normal. An enormous cystic liver (9510 gm.) was found at postmortem. Small areas of parenchyma were noted between the cysts in the kidneys. No renal tissue was preserved for microscopic study.

CASE 30. The patient died in coma following a fracture of the humerus. The urine was bloody. On section all parts of the kidneys were filled with cysts 3 mm. to 2.5 cm. in diameter. There was practically no persistent parenchyma (Fig. 1).

The septa between the cysts show occasional normal glomeruli and tubules, but for the most part they are composed of dense fibrous tissue with remnants of hyaline glomeruli. The arteries usually show a marked fibrous intimal thickening and medial fibrosis. The arterioles show chiefly a marked medial fibrosis. The changes in the vessels suggest disuse atrophy. The numerous hyaline glomeruli in the septa are probably the result of pressure atrophy.

CASE 31. Duration of symptoms about 9 weeks; weakness, anorexia and loss of weight. The urine showed a trace of albumin. Several convulsions on the day before death. On section the parenchyma of the kidneys was almost completely replaced by cysts, only small islands of cortex near the capsule were found.

Microscopic sections through the solid areas of cortex show large glomeruli and large dilated tubules that are normal, except for the hypertrophy. There is marked atrophy of the parenchyma between and around the cysts. The arterioles are normal and the arteries show only the usual changes associated with age. Small areas of interstitial fibrosis are seen in which the connective tissue is too abundant and dense to be explained as a mere replacement fibrosis from atrophy of tubules. Atrophy seems to be due entirely to expansion of the cysts.

CASE 32. The patient had not been well for 10 years, but had been acutely ill for only 3 months. He complained of weakness, loss

of weight, enlargement of the abdomen with a dull aching pain in the upper part, and hematuria. He had had several attacks of hematuria during the preceding 18 months. One brother and one sister have some form of renal disease. There was a marked secondary anemia. Only small islands of cortex were found in the kidneys which were almost completely replaced by cysts. No renal tissue was preserved for microscopic examination.

CASE 33. The patient stated that he had felt well until August 4th, 3 weeks before death. He complained of weakness and dizziness and soon became irrational. He was in coma the last few days of his life. At postmortem a glioma, 7 cm. in diameter, was found in the right frontal lobe. On section the kidneys showed only a few small islands of cortex. There were thin septa between the cysts.

In the islands of intact cortex the arterioles show the hyaline intimal layer characteristic of hypertension, but the destruction of parenchyma is due entirely to the cysts and not to arterial disease. The cysts show papillary epithelial ingrowths. The glomeruli show a definite increase of endothelial cells and some thickening of the capillary basement membranes.

CASE 34. Five years before his death the patient sustained fractures of the pelvis, ribs and legs in an accident. The urine was bloody at that time. One year later he began to have attacks of pain in the right flank, accompanied by nausea, vomiting and weakness. Seven months before his death he had a severe attack and was admitted to the hospital. There were many red blood cells in the urine and the phenolsulphonephthalein output was zero. The blood urea nitrogen was 128 mg. per 100 cc. at that time. Subsequent study showed no special features. The albumin in the urine varied from a trace to a large amount. There was some blurring of vision. The eyegrounds showed some tortuosity of the arteries but no hemorrhages or exudates. The kidneys were palpable. On section the kidneys showed only a few islands of persistent cortex. The cysts were separated by thin septa and many of them contained blood.

Microscopically no normal parenchyma is found. The cysts are usually surrounded and separated by dense fibrous tissue which contains only remnants of tubules and hyaline glomeruli or is purely fibrous in structure. In the larger areas between the cysts there is an

interstitial fibrosis and the majority of the glomeruli are either entirely hyaline or they show patches of hyaline degeneration due to thickening of the capillary basement membranes. The changes in the glomeruli are not due to obstruction of the arterioles; they are probably caused by pressure of the cysts or by focal glomerulitis.

CASE 35. The patient had occasional attacks of pain in the right flank for 2 years preceding his death. On March 5, 1934, he had an attack of hematuria which lasted several days. Both kidneys were enlarged and the right was tender. Death, April 6, 1934. On section the parenchyma of the kidneys was almost completely replaced by cysts, and many of the cysts were filled with purulent or gangrenous material. No tissue from the kidneys was preserved.

CASE 36. The patient died 3 hours after admission to the hospital and had not been under medical care previously. She was in coma and had seven convulsions during 3 hours. The urine contained a large amount of albumin. On gross examination of the kidneys a few small, irregular islands of cortex were found. There was pus in some of the cysts.

In the solid areas there is a marked interstitial fibrosis. Many of the tubules are atrophic but others are large and dilated. There are many hyaline glomeruli surrounded by old fibrous crescents. The arterioles show advanced medial fibrosis, but their lumens are large (Fig. 4). The destruction of the parenchyma is not due to arterial disease, but to the cysts, interstitial fibrosis and an old glomerulonephritis.

CASE 37. The patient complained of weakness, abdominal pain, headache and dizziness. She had a convulsion shortly before death. On section of the kidneys only small, irregular areas of parenchyma were found.

These areas show severe interstitial fibrosis in some parts. The few normal tubules are greatly hypertrophied. There is no evidence that atrophy is due to arterial disease. There is a marked medial fibrosis of the arterioles (Fig. 5). The hyaline glomeruli seem to be due to pressure atrophy of the tissue resulting from expansion of the numerous cysts.

CASE 38. The patient had had hypertension for about 10 years. She had been in as good health as usual when she became uncon-

scious during the night and died the following day. She was not paralyzed. The urine showed a specific gravity of 1008 and a trace of albumin. The parenchyma of the kidneys was almost completely replaced by cysts varying in diameter from 1 mm. to 4 cm. No renal tissue was preserved for microscopic study.

CASE 39. The patient had complained of visual disturbances for many years. During the past 2 years she had had dyspnea, swelling of the ankles, dizziness and hypertension. Many attacks of nausea and vomiting during the past year. Polyuria during the fall of 1931. Admitted to the hospital Dec. 17, 1931. Died 2 days later. Hemoglobin, 55 per cent. Moderate albuminuria. The kidneys were filled with cysts and contained very little solid parenchyma. No renal tissue was preserved.

CASE 40. The patient had an attack of hematuria about 3 years before his death. He had no other symptoms until Nov. 20, 1932, when he developed weakness and edema of the ankles following a "cold." Later he developed dyspnea and nausea which persisted. Hemoglobin 65 per cent. Slight albuminuria. Death, Feb. 13, 1933. On section the kidneys consisted almost entirely of cysts separated by thin septa. The largest solid areas of parenchyma were less than 1 cm. in thickness.

There is a very marked interstitial fibrosis. No areas of normal tissue are found microscopically. The arteries show a pronounced intimal thickening. The arterioles show hyaline degeneration of the media but no narrowing of their lumens. There is no evidence that any atrophy is caused by vascular disease; the growth of the cysts and the fibrosis of the interstitial tissue seem responsible for the destruction of the parenchyma.

CASE 41. The patient developed a sudden paralysis of the right arm and leg in August, 1930. He was under hospital care for hemiplegia and hypertension. The kidneys were palpable. There was a large amount of albumin in the urine toward the end of his illness. Death, Sept. 15, 1933. On section the kidneys showed only occasional small masses of solid tissue between the cysts.

Microscopic sections of these areas show extreme fibrosis of the interstitial tissue. The arteries and arterioles show a very marked fibrosis of the media, but no narrowing of the lumens. There are

some normal glomeruli. The hyaline glomeruli are apparently the result of pressure from the dense interstitial tissue.

CASE 42. In March, 1934, the patient first consulted a physician because of loss of weight, dyspnea and swelling of the ankles. At this time the hemoglobin was 60 per cent, there was a very low excretion of phenolsulphonephthalein, and the blood pressure was 170/110. She was admitted to the hospital on April 17, 1934. The urine showed albumin +, many pus cells and a specific gravity of 1010. May 6th, stupor and muscular twitching developed. Death, May 8, 1934. On section the parenchyma of the kidneys was almost completely replaced by cysts. No islands of normal parenchyma were found.

Microscopic sections of small solid areas between the cysts show a marked interstitial fibrosis and extensive atrophy of parenchyma, but there are some large normal glomeruli and tubules. The arteries show an extreme elastic-intimal thickening which narrows the lumens to a marked degree. The terminal arterioles show only occasional bands of subintimal hyalin. Some of the hyaline glomeruli are apparently the result of the arterial disease, others are caused by pressure atrophy.

CASE 43. A diagnosis of "Bright's disease" had been made 12 years previously, but no details of the symptoms at that time were available except that he was confined to bed for 1 year. He was treated for gastric ulcer in February, 1930, and at that time he had a definite renal insufficiency — phenolsulphonephthalein output 20 per cent in 2 hours, blood urea nitrogen 75.6 mg. He was fairly comfortable from that time until about May 1, 1930, when he developed great weakness and vomiting. He had dyspnea on exertion and slight edema of the lower extremities. He had never noted hematuria. A severe degree of renal insufficiency finally developed. He remained in the hospital until his death, Oct. 10, 1931. In the left kidney one could not distinguish cortex from medulla. Three calyces were traced into cysts. There was no normal renal parenchyma. The right kidney, which was the smaller, showed some islands of fairly normal parenchyma. The cysts occupied both the cortex and the medulla. These were typical polycystic kidneys but they were only slightly enlarged. The heart was enormously enlarged.

Microscopically there is a severe disease of the arteries and arte-

rioles with advanced atrophy of the parenchyma due to the arterial disease. The principal change in the arteries is an intimal thickening which is largely composed of collagenous tissue. The glomeruli are in various stages of hyaline degeneration due to thickening of the basement membranes of the capillaries. Many of the glomeruli show also an endothelial increase characteristic of primary hypertension with renal insufficiency (malignant hypertension). The extremely tortuous arteries are evidence that the kidneys were originally much larger. The cysts evidently played an unimportant rôle in the destruction of the parenchyma. The best interpretation of this kidney is a primary hypertension superimposed on a cystic kidney.

CASE 44. The duration of the patient's illness was indefinite. He did not complain of dyspnea or cough but there was a moderate pitting edema of the lower extremities. The hemoglobin was 50 per cent. Albumin in the urine o to +. The eyegrounds showed tortuous arteries and some exudate but no hemorrhages. The heart was greatly enlarged. Coma developed and the patient died 1 week after admission. On section the thin cortex of the kidneys was closely studded with small cysts. There were no cysts in the medullary portions.

There is an extreme elastic and collagenous intimal thickening of the arteries and arterioles and the great majority of the glomeruli are hyaline or in a stage of hyaline degeneration due to thickening of the capillary basement membranes. A few glomeruli show the endothelial proliferation characteristic of primary hypertension with uremia (malignant hypertension). The cysts are for the most part dilated hypertrophic tubules (Fig. 6). Tubules may be traced into cysts, and all transitions may be found between normal tubules and large cysts. The interpretation of this kidney is primary hypertension with atrophy of most of the parenchyma and subsequent hypertrophy and dilatation of persistent tubules to form cysts. There is no evidence that it is a true congenital cystic kidney. The absence of cysts in the medulla is very significant since the medulla is nearly always cystic in the congenital cystic kidney. Greene's case of renal rickets, mentioned above, is apparently a dilatation of persistent tubules in an atrophic or hypoplastic kidney.

CASE 4. The unilateral polycystic kidney (No. 4, Table IV) may be discussed with this group. The patient was admitted to the hos-

pital, Dec. 6, 1933, for a traumatic fracture of the left tibia and fibula. Her blood pressure was 140/72 at that time. The fracture failed to heal. In April, 1934, the blood pressure was 195/110 and there was slight edema of the ankles. The blood pressure varied from time to time between 140/80 and 195/110. The hemoglobin was 85 per cent, and there was occasionally a trace of albumin in the urine. She died May 24, 1934, with signs of apoplexy. At postmortem there was found softening of the left temporal lobe from arterial thrombosis. The right adrenal was replaced by a hypernephroma weighing 435 gm. The right kidney was of normal structure. The left kidney weighed 666 gm. and was filled with cysts. There was a fair amount of normal parenchyma at one pole.

Microscopically there is atrophy around and between the cysts, but the solid areas have a normal structure. The arteries in both the normal and the cystic kidneys show a fairly marked, elastic-intimal thickening and the arterioles in both kidneys show a hyaline intimal thickening. The changes in the arteries and arterioles are typical of hypertension and there are no differences in the vessels of the two kidneys.

Changes in the Arteries and Arterioles

Several writers have commented on the condition of the arterial system in the polycystic kidney. Meader, 1907, in a stillborn infant found the arteries quite large and their walls extensively thickened. McKinlay, 1920, in a male 30 years of age, with a very high blood pressure, noted that the arterioles frequently showed great thickening and hyalinization of their walls. Staemmler, 1921, in a stillborn infant, observed thickening of the walls of arteries and arterioles but no changes in the intimal layer.

Ritter and Baehr, 1929, made an excellent study of the arterial system by injecting the vessels with a mixture of barium sulphate and gelatin and then clearing the specimen. They injected kidneys from three cases and found that the interlobular and intralobular arteries lie largely in the walls of cysts and that they are greatly elongated because of the increased size of the kidney and their tortuous course around the cysts. The injected kidneys showed a disappearance of the finer arterial branches. These investigators believed that they were dealing with a typical, well developed arteriolo-

sclerosis and that arterial disease was responsible for the destruction of the persistent islands of parenchyma in the polycystic kidney.

Podgurski, 1930, paid special attention to the arteries in 7 cases of polycystic kidneys in adults. He noted that the arteries and arterioles were "thick-walled and sclerotic." He called attention to hypertrophy of the media in 1 case, and elastic-intimal thickening in another. In 3 cases there was pronounced arteriolosclerosis and 2 of these were interpreted as true hypertension.

Braasch and Schacht, 1932, stated that there is usually a marked thickening of the arteries and arterioles. Their illustration shows an artery with no intimal disease but apparently with hypertrophy of the media.

A thorough study of our material has been made to determine the structural changes responsible for the thick walls of the vessels and the relation of this process to other forms of arterial disease. In the group of newborn infants we found normal arteries and arterioles in all instances except one. In this case the larger arteries showed a definite medial fibrosis which caused the walls to appear somewhat hyaline. There was no intimal disease. In the subclinical group, Table VI, the arterial changes correspond with the age of the patient and no effect of the cystic disease can be seen.

In the clinical group there are a number of cases in which the arterial changes are in excess of processes attributable to age. The degree of intimal thickening and medial fibrosis in the arteries and arterioles is indicated in Table VII — Grade 3 representing the maximum degree of the process.

The Arteries: (*A*) The intima shows a high degree of intimal thickening in 8 cases (Grade 3 in Table VII). The lesser degrees of involvement are explainable on the basis of age. The thick intima is responsible for the "thick-walled" appearance of the arteries noted by several observers. Elastic tissue stains show that the thick intima contains several coarse elastic lamellae, and the azocarmine stain shows a large amount of collagenous tissue in addition to the elastic layers. Occasionally a large artery is almost completely closed by a layer of collagenous tissue inside the elastic layer (Fig. 3). The elastic laminae may be torn and fragmented, indicating retrogressive changes. The significance of this intimal thickening is not entirely clear. It is known that hypertension tends to cause elastic intimal thickening, but the large amount of collagenous tissue fre-

quently seen suggests that some other factor is also concerned. It is possible that disuse atrophy is partly responsible for the thickened intima. In the atrophic kidneys of chronic glomerulonephritis the arteries often show a similar structure. It is believed that the intimal thickening is compensatory in that it reduces the lumen to a size consistent with the decreased blood flow. In the polycystic kidneys a large proportion of the glomeruli and tubules have disappeared, leaving only cysts and fibrous tissue which require much less blood.

(*B*) The media of the arteries shows some degree of fibrosis in most instances but not in excess of that found in normal kidneys of persons of corresponding age, except in one instance, Case 41, in which it is very pronounced. With a high degree of medial fibrosis the media of the artery has a glassy hyaline appearance.

The Arterioles: In the arterioles medial fibrosis is often prominent (Figs. 4 and 5). In a few instances definite hyaline masses are seen in the media. Aside from the 2 cases of true hypertension (Cases 43 and 44) there is relatively little intimal disease in the arterioles, and their lumens are widely patent. The typical arteriolosclerosis associated with hypertension is characterized by a subintimal hyaline deposit. The arteriolar disease in polycystic kidneys differs from this since it is chiefly fibrosis and hyalinization of the media with a normal intima.

Case 44 is not a true polycystic kidney but a cystic dilation of persistent hypertrophic tubules in a hypertensive kidney. Case 43 is apparently true primary hypertension superimposed on a polycystic kidney. Aside from these 2 cases the arterial disease is responsible for very little atrophy in the persistent islands of parenchyma of the polycystic kidney. In fact, the arterial disease is more readily explained as an effect than as a cause of atrophy. The great increase in the length of the arteries and their tortuous courses around the cysts probably alter their structure. The other influences affecting the arteries are the increased blood pressure and the decrease of functioning parenchyma which they supply.

That the veins of the kidneys are sometimes obstructed is indicated by Duskes' report in which an extensive collateral venous circulation was described.

Hypertension in polycystic renal disease is to be attributed to increased resistance to the flow of blood through the kidneys or to anemia. This same principle applies in glomerulonephritis. The

experimental work of Goldblatt and his collaborators indicates that anemia of the kidney is more important than resistance to blood flow in causing hypertension. It is possible that obstruction in the renal circulation or anemia of the kidneys brings about reflex stimulation of the vasomotor center which results in a generalized increase of vascular tonus.

Etiology and Pathogenesis

It will not be necessary to review the older theories of the origin of polycystic kidneys; we may begin with the theory proposed by Ribbert. A discussion of the earlier theories may be found in Braunwarth's paper. After the embryologists had established the separate origin of the collecting and convoluted tubules, Ribbert offered the hypothesis that convoluted tubules fail to unite with the collecting tubules and subsequently develop into cysts. This interpretation gained widespread acceptance for many years, but has now been disproved clearly by Kampmeier's investigations.

That the polycystic kidney is due to a developmental defect is indicated by the associated anomalies that are commonly present in the newborn group. One may find anencephaly, spina bifida, encephalocele, myelocele, craniorachischisis, undescended testes, club foot, anomalies of the internal genital organs in the female, and so on. Cysts are frequently found in the liver and occasionally in the pancreas also (Rümler). There is no doubt that true polycystic kidneys are always congenital in origin and definitely hereditary.

In order to understand the modern theory of the origin of the congenital cystic kidney it is necessary to be familiar with the normal organogenesis of the kidney. The primitive outgrowths from the renal pelvis divide and subdivide repeatedly to form collecting tubules. Each division of the collecting tubules is referred to as a generation, *e.g.* first generation, second generation, and so on. Each newly formed collecting tubule from the first generation onward comes into contact with the metanephric blastema — an undifferentiated cellular mesenchymal tissue. The blastema forms a cap over the end of the collecting tubule and differentiates into a curved solid structure, the primitive convoluted tubule. A lumen soon forms in the solid tubule and opens into that of the collecting tubule. Commonly the opposite end of the short convoluted tubule develops a

glomerulus. The first three or four generations of convoluted tubules are not permanent, they become detached from the collecting tubules and persist for a time as cystic structures usually provided with a glomerulus. The generations of tubules after the third or fourth are permanent. In the early embryonal period there are, therefore, numerous cysts in the kidneys formed from the first few generations of tubules. McKenna and Kampmeier have made numerous reconstructions of these cysts. Normally these fetal cysts atrophy but their persistence offers the simplest explanation of the origin of single and multiple cysts in the adult kidney.

A fundamental objection to the "failure of union" theory is that the metanephric blastema does not develop into a tubule until after it has joined the collecting tubule. At least there is no satisfactory evidence that any differentiation of the metanephric blastema occurs when the collecting tubules do not penetrate it.

The various stages in the development of the polycystic kidney have not been worked out but it is probable that the first stage is a persistence of the fetal cystic structures arising from the first generations of collecting tubules. It is possible that many of the primitive tubules fail to become detached and thus prevent the subsequent formation of collecting tubules. The rarity of collecting tubules in polycystic kidneys supports this hypothesis. On the basis of Kampmeier's theory we can understand why a cyst often contains a glomerulus in its wall and why a normal tubule frequently opens into a cyst; the detached primitive tubule differentiates into glomerulus and tubule and a part or all of the tubule becomes cystic. Since the glomeruli of the detached tubules have a normal blood supply the secretion of urine would tend to cause cystic dilatation of the tubules.

An outstanding feature of the polycystic kidney is the marked reduction in the number of functioning units or nephrons. When death occurs in early infancy it is found that the number of normal nephrons is insufficient to maintain life. But since a great many persons with polycystic kidneys live until middle life or later we may ask — what was the structure of their kidneys at birth? And what changes did they undergo between birth and the final termination in uremia? We have only incomplete answers to these questions — the various stages in the development of the polycystic kidney have not been identified. We know that the kidneys become progres-

sively larger. Numerous writers have observed great increases in size over a period of years or months. It is also fairly clear that this increase in size is due largely if not entirely to an increase in the size of the cysts and not to an increase in number. The stages immediately preceding renal insufficiency have been identified; our subclinical group (Table VI) contains examples of this type. These kidneys differ from those with renal insufficiency in that they show larger areas of parenchyma not yet replaced by cysts. The continued expansion of the cysts in this subclinical group would destroy more parenchyma and bring on renal insufficiency. Stieda described an excess of connective tissue in the medulla in a subclinical case. Although the stages have not been identified it is highly probable that polycystic kidneys at birth have a still greater proportion of intact parenchyma than is found in the subclinical group at postmortem. In childhood and youth the persistent islands of parenchyma hypertrophy and compensate for the tissue destroyed by the cysts. This is probably the reason why there are so few deaths between infancy and the third decade. But in adult life the ability to hypertrophy is greatly decreased, parenchyma is destroyed more rapidly than it can be replaced and the patient progresses toward renal insufficiency.

The destruction of parenchyma is due largely to the cysts. An associated hypertension, as in Case 43, or glomerulonephritis as in Case 36, may destroy the islands of parenchyma, but these complications are unusual. The destructive effects of pressure are easily observed between and around the cysts. The tortuous thick-walled arteries and the elevated blood pressure probably contribute to some extent to the destruction of the parenchyma. The expansion of the cysts produces a pressure atrophy of the tubules and glomeruli. The abundant interstitial tissue, especially in the medulla, becomes more dense and fibrous with age and also compresses the tubules. Some of the smaller cysts in adult kidneys represent hypertrophy of persistent tubules, or they may be tubules that originally communicated with the pelvis which were later obstructed by the pressure of connective tissue or cysts. The great majority of the larger cysts are probably of fetal origin.

Cystic kidneys are frequently found in the horse and pig, rarely in the cat and wild animals (Hartoch).

Summary

Polycystic kidneys are found once in about every 500 post-mortems, and from 5 to 10 per cent are unilateral.

In our autopsy service about one-third of the cases occurred in infants, the majority of which were stillborn.

There are relatively few clinical cases between infancy and the age of 25 years, but the disease is always congenital.

We may distinguish a surgical type in which the patient presents symptoms and signs referable to one kidney, *viz.* pain, tumor, hematuria, infection, and so on.

In the medical type the symptoms are those of acute or chronic renal insufficiency, and the functional disturbances correspond to those of contracted kidneys. Attacks of hematuria are, however, distinctive.

Edema is rarely prominent, and cardiac failure is unusual.

The systolic blood pressure is 150 mm. Hg or higher in over 50 per cent of the cases that have been reported, and hypertension is somewhat more frequent in advanced than in early stages of the disease.

Cardiac hypertrophy often develops but is much less pronounced than in primary hypertension.

Retinal changes of the hypertensive type may be found, especially in those with very high blood pressure.

Some patients live many years after symptoms have developed.

When the renal reserve is low, *i.e.* in advanced cases, pregnancy causes a typical nephritic toxemia, but there is no disturbance when the renal reserve is good.

There is abundant evidence that polycystic renal disease has a strong hereditary tendency.

The pyelogram is of great diagnostic value in cases where the diagnosis is otherwise difficult.

In the newborn group the outstanding structural changes are the presence of numerous cysts, hypoplasia of parenchyma, *i.e.* a great reduction in the number of nephrons, and an excessive amount of interstitial connective tissue.

The numerous "glomerular" cysts are interpreted as vestigial structures derived from the first three or four generations of tubules.

In the subclinical group there is abundant renal parenchyma

between the cysts, while in the clinical group the parenchyma may be reduced to a few small scattered islands.

The progressive atrophy of the parenchyma is brought about chiefly by continuous expansion of the cysts. Arterial disease plays a minor rôle in this process, except in the occasional case in which true primary hypertension is superimposed on the cystic disease.

The arteries usually show a marked intimal thickening which is attributed chiefly to disuse atrophy but partly to hypertension. Medial fibrosis in the arteries is explainable on the basis of age.

The arterioles show no marked intimal disease except when primary hypertension is a complication. However, they often show a marked medial fibrosis. This process is not true arteriolosclerosis.

Kampmeier's theory of the origin of the cysts is favored.

One case is described (Case 44) in which compensatory dilatation of persistent tubules in a hypertensive contracted kidney caused it to resemble the true congenital cystic kidney.

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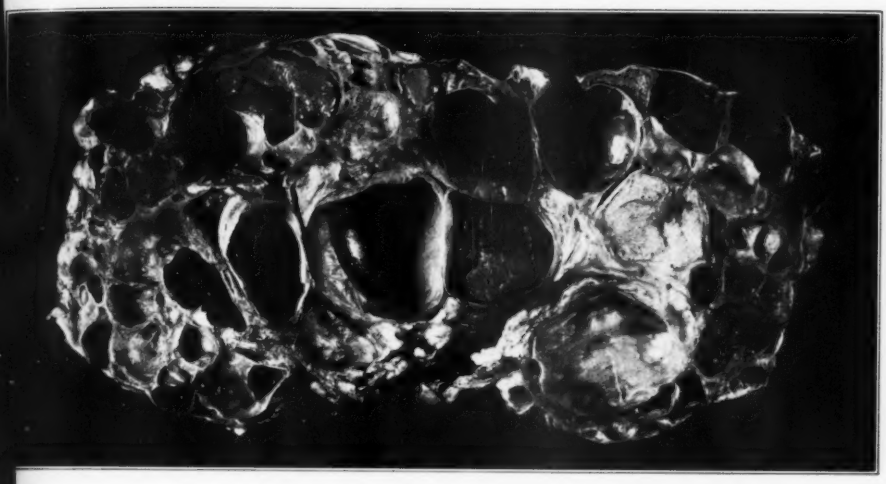
DESCRIPTION OF PLATES

PLATE 56

FIG. 1. Case 30 (Table VII). Section of a kidney from a patient who died of uremia. No islands of normal parenchyma are present.

FIG. 2. Case 24 (Table VII). Section of a kidney from a patient who died of bacterial endocarditis. There was some renal insufficiency. Note the large areas of persistent parenchyma.



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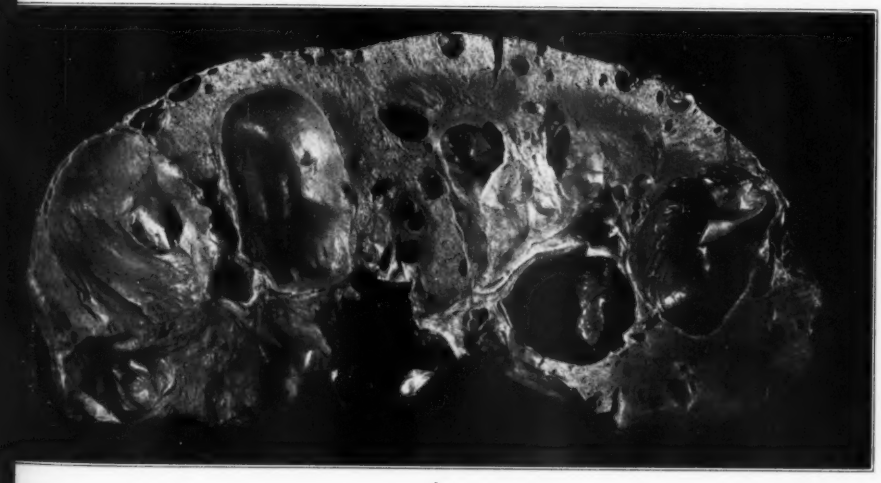


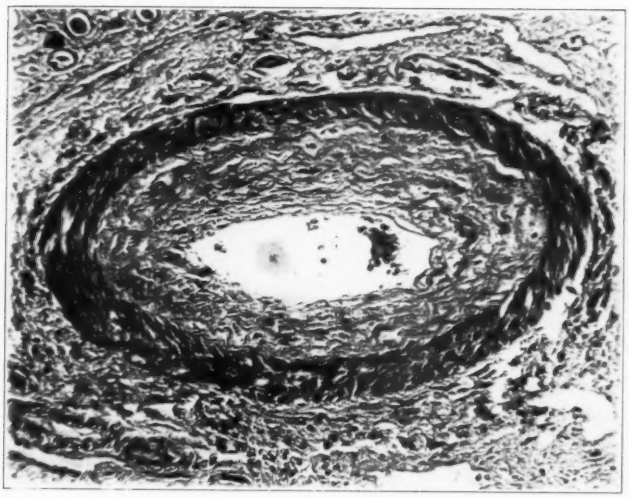
2

Bell Cystic Disease of Kidneys

PLATE 57

FIG. 3. Case 2 (Table VII). Medium sized renal artery showing a high degree of intimal thickening. The intima is composed of both elastic and collagenous fibers.

FIG. 4. Case 36 (Table VII). Arteriole showing extreme medial fibrosis. The wall consists entirely of collagenous fibers which appear black in the illustration. There are no muscle fibers or elastic fibers. The intima is normal. Mallory-Heidenhain stain.



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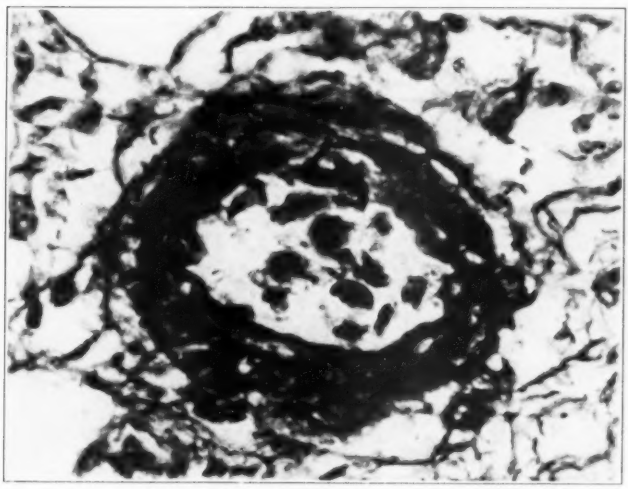
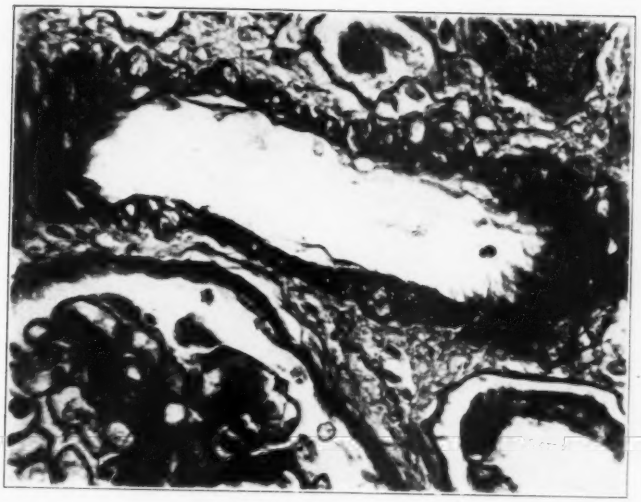


4

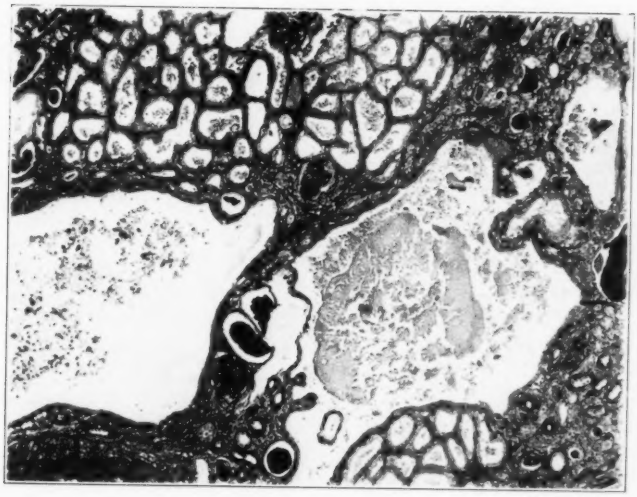
PLATE 58

FIG. 5. Case 37 (Table VII). Arteriole showing extreme medial fibrosis. Nuclei of muscle fibers are seen (the clear rounded areas), but no muscle sarcoplasm is present. The wall is composed entirely of collagenous fibers (black). The intima is normal. The lumen is dilated. Mallory-Heidenhain stain.

FIG. 6. Case 44 (Table VII). Hypertensive kidney with multiple cysts formed by dilation of tubules. These are not congenital cysts.



5



6

THE LIPID CONTENT OF LIVERS OF NON-IMMUNIZED AND IMMUNIZED HORSES *

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Prolonged or intensive immunization of horses for the production of therapeutic serums is so often complicated by fatty degeneration or even rupture of the liver, that a chemical and histological study was made of the tissue changes and of the extent of the degenerative processes in this organ. It is the purpose of this paper to record the observations made in the course of these studies. Further investigation of the lipid constitution of the blood, plasma and serum will be recorded in a second paper.

A number of investigations have been made of the chemical nature of the fatty changes in the liver. In 1914 Imrie [1] examined human livers. The method of procedure for the estimation of fats consisted in saponifying the tissue with potassium hydroxide. To the saponified digest, sulfuric acid was added to liberate the fatty acids, which were extracted with petroleum ether and evaporated; the residue was weighed. No corrections were made for cholesterol. It is evident that the fatty acids contained in the phospholipids are a part of the fatty acids determined. The significance of the phospholipids was not considered in Imrie's work.

Theis [2, 3, 4] concluded from his investigation that there is a definite and quite constant correlation between the phospholipids and the total fatty material in normal liver tissue, and proposed the equilibrium equation phospholipid $\rightleftharpoons$ neutral fat. In abnormal conditions he found that "there may be either a change in total lipid content or more generally a shift to the right of the phospholipid-neutral fat ratio." [4] The distribution ratio in beef liver he reported as 55 per cent phospholipid : 45 per cent neutral fat. Apparently a variation of 10 per cent in the ratio was not considered significant by Theis. The lipids of two human livers accepted as normal had ratios of 50 per

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cent phospholipid: 50 per cent neutral fat and of 59:41, while two abnormal fatty livers had a ratio of 45 : 55 and 17 : 83. Theis obtained only about 75 per cent phospholipids in the extracted solids. This may have been due in part to incomplete precipitation of phospholipids on adding acetone to the ether solution of the lipids. MacLean and Williams,[5] also MacLean and MacLean,[6] found that the phospholipids may form as much as 84 per cent of the total fat and questioned the presence of any true fat.

The determination of lipids in horse liver tissue, as planned for this investigation, involved the estimation of total fatty acids, phospholipids, free and esterified cholesterol, and the iodine value of the total fatty acids. The extraction of the lipids was made with boiling alcohol and ether [7] and is recognized as the Bloor procedure. The determination of total fatty acids and phospholipids was also based on Bloor's methods.[8] In the estimation of phospholipids, the phosphorus was determined in the petroleum-ether extract and calculated to lecithin. The phosphorus was precipitated and weighed as ammonium phosphomolybdate. The method used is essentially that described by Elek.[9] This procedure supplanted the acetone and magnesium chloride precipitation as practiced by Bloor.[10] The Osato and Heki [11] methods, with slight modifications, were used for the estimation of free and esterified cholesterol. The iodine values of the total fatty acids were determined by the Rosenmund and Kuhnhenn pyridine-dibromide method, as practiced by Yasuda.[12] All results obtained in the lipid work were determined by micromethods. The estimation of neutral fats (triglycerides) was made by calculating the fatty acids in the phospholipids (taken as two-thirds of the weight) and the cholesterol ester (esterified cholesterol × 0.734). The sum of the fatty acids in the phospholipids and the cholesterol was subtracted from the total fatty acids. The residual fatty acids multiplied by the factor 1.045 gave the neutral fat.

VARIATION IN DUPLICATE ANALYSES

	No.	Average
		%
Total fatty acids	49	2.9
Phospholipids	25	1.7
Total cholesterol	23	1.6
Free cholesterol	24	1.8

With a few exceptions at the beginning of the study, the analyses were done in duplicate and, in order to record the accuracy of the data, the above tabulation has been compiled.

The livers from 8 non-immunized and 41 immunized horses were studied. The immunized animals included 11 tetanus, 6 diphtheria, 1 botulinus, 7 meningococcus, 12 pneumococcus, and 4 streptococcus horses. One horse which was not immunized but had parasitic infestation died. The analysis of this liver is appended to record the changes found in this condition; likewise that of a donkey which had been immunized, first with sheep cells and then with *B. abortus*. Some of the horses had been immunized with various cultures and toxins; that used last determined the classification. Two of the horses studied were not under active immunization at the time of death and are classified as "resting." The results of the chemical analyses are recorded in Tables I and II.

TABLE I

Variation in the Lipid Content of the Livers of Non-Immunized and Immunized Horses

	Number of horses		
	6 non-immunized	2 resting	41 immunized
	range	*range*	*range*
Total fatty acids ..... %	2.48–2.82	2.63–2.73	1.82–9.12
Total fatty acids iodine value.. %	90.2–96.7	97.0–104.9	77.1–103.3
Phospholipids ..... %	3.24–4.55	3.68–3.87	1.41–4.30
Free cholesterol ..... %	0.159–0.216	0.177–0.199	0.169–0.262
Esterified cholesterol ..... %	0.010–0.030	0.007–0.032	0.007–0.493
Neutral fat ..... %	0.25–0.54	0.14–0.15	0.15–5.75

The percentage of the total fatty acids in the non-immunized and resting horses varied but little; in the immunized horses the variation was quite pronounced. The iodine values indicated a quite uniform degree of unsaturation. The amount of phospholipids of the non-immunized and resting horses varied only slightly, while that of the immunized horses showed appreciable differences in percentage and, with few exceptions, was uniformly less. The free-cholesterol values in the non-immunized and resting horses were similar; with the immunized horses the range was higher. The esterified cholesterol was

TABLE II

The Distribution of Lipids in the Livers of 8 Non-Immunized and 41 Immunized Horses

		Horse No.	Sex	Age	Death*	Period of immunization	Total fatty acids: Per cent	Total fatty acids: Iodine value	Phospholipids	Free cholesterol	Esterified cholesterol	Neutral fats	Ratio phospholipids: neutral fats	Ratio phospholipids: free-cholesterol	Scharlach R staining†	Titer of serum: Maximum	Titer of serum: Final
				yrs.		*yrs. mos.*			*per cent*	*per cent*	*per cent*	*per cent*	*per cent*			*units*	*units*
Non-immunized		417	M	28	BS				4.55	0.216	0.020			21.2:1			
		435	F	23	BS		2.48	91.3	3.24	0.159	0.030	0.31	91:90	20.3:1	±		
		416	M	23	S				4.05	0.202	0.017			19.8:1			
		425	F	22	BS		2.82	96.7	3.87	0.196	0.014	0.25	94:60	19.8:1	+		
		436	M	23	BS		2.69	95.1	3.24	0.172	0.021	0.54	86:14	19.0:1	±		
		408	F	27	BC		2.58	90.2	3.50	0.191	0.010	0.25	93:70	18.2:1	±		
	Resting‡	294	M	8	BS		2.63	104.9	3.68	0.177	0.032	0.14	96:40	20.7:1	±		
		363	M	18	BS		2.73	97.0	3.87	0.199	0.007	0.15	96:40	19.4:1			
	Average						2.66	95.9	3.75	0.189	0.019	0.27	93:70	19.8:1			
Immunized	*B. tetanus*	418	M	5	BS	10	3.35	94.8	4.30	0.235	0.021	0.49	90:10	18.2:1		660	270
		401	M	7	BS	5	2.58	95.8	3.37	0.200	0.025	0.33	91:90	16.9:1	+	10 +	10 +
		374	M	20	BS	10	2.77	98.5	3.27	0.195	0.048	0.58	85:15	16.9:1	2 +	310	180
		329	M	19	BS	2	2.67	100.0	3.39	0.210	0.033	0.40	90:10	16.2:1	±	650	460
		385	F	16	BS	10	3.08	90.3	3.31	0.231	0.020	0.91	79:21	14.4:1		1130	1130
		345	M	23	D	6	3.95	77.1	2.99	0.232	0.017	2.04	59:41	12.9:1	3 +	350	300
		320	M	20	BS	2 8	2.48	90.3	2.42	0.191	0.168	0.77	76:24	12.7:1	2 +	900	410
		356	M	24	BS	1 7	2.22	103.3	2.52	0.204	0.122	0.51	84:16	12.3:1	+	500	300
		339	M	5	BC	1 4	2.76	88.4	2.46	0.262	0.276	0.96	72:28	9.4:1		560	300
		325	M	20	DR	2 5	1.83	93.5	1.63	0.214	0.138	0.67	70:30	7.6:1	2 +	850	850
		354	M	17	DR	1 8	1.82	96.9	1.66	0.246	0.021	0.73	69:31	6.8:1		1000	940
	B. diphtheriae	409§	M	17	BS	2½	3.92		3.84	0.234	0.029	1.40	73:27	16.5:1		5	1 ±
		412§	M	17	BS	3	2.78	97.1	3.19	0.228	0.036	0.67	83:17	15.7:1		325 ±	100 ±
		463**	F	9	D	½	7.14		2.41	0.169	0.048	5.75	30:70	14.4:1			
		421**	F	4	D	½	3.80		2.92	0.205	0.018	1.92	60:40	14.2:1			
		155	M	21	BS	1½	2.93		3.22	0.259	0.023	0.81	80:20	12.5:1		750	750
		380**	M	2	D	½	2.63		2.36	0.194	0.024	1.09	69:31	12.0:1			
	B. Botulinus	271	F	20	BS	4 7	2.59	93.6	3.57	0.236	0.012	0.20	95:50	15.1:1		550	100

B. Bovi-linus	371	F	28	BS	4 7	2.59	93.6	3.37	0.230	0.012	0.20	93.30	13.1:1		330	100

Immunized	Meningococcus	389	M	13	D	11	1.97	95.5	2.61	0.181	0.024	0.22	92:80	14.4:1		ap. stand.	low
		287	M	18	BS	3 11	2.50	86.0	2.82	0.217	0.049	0.62	82:18	12.9:1	2+	high	ap. stand.
		352	M	3	BS	3	2.96	90.1	2.75	0.225	0.024	1.04	73:27	12.2:1	+	low	low
		370	M	15	BC	1 1	2.26	93.3	2.61	0.221	0.007	0.54	83:17	11.8:1	+	high	low
		375	M	17	D	10	2.63	84.5	2.43	0.205	0.031	1.03	70:30	11.8:1	3+	high	high
		347	M	22	BDR	1 11	2.79	92.2	2.33	0.255	0.229	1.12	68:32	9.1:1	5+	high	low
		357	F	24	DR	1 10	3.27	94.5	1.41	0.261	0.294	2.21	61:39	5.4:1	4+	high	high
	Pneumococcus	448	M	15	*	8	2.62		3.22	0.210	0.025	0.47	87:13	15.4:1		ap. stand.	ap. stand.
		359	M	18	S	2	4.71	82.1	3.92	0.253	0.030	2.17	64:36	15.4:1	4+	high	ap. stand.
		397	M	24	BC	1	3.10	87.6	3.48	0.231	0.018	0.80	81:19	15.1:1		ap. stand.	low
		430	F	17	D	4	4.52	84.8	3.21	0.213	0.029	2.46	57:43	15.1:1		low	low
		453	M	18	D	1	2.48	93.9	2.75	0.189	0.027	0.66	81:19	14.6:1		low	low
		434	F	17	BS	8	2.96	92.9	3.76	0.258	0.009	0.47	89:11	14.6:1		ap. stand.	ap. stand.
		342	M	5	BS	2 9	3.18	101.0	3.58	0.248	0.008	0.82	81:19	14.4:1		high	low
		451	F	21	S	6	9.12		3.33	0.238	0.098	0.71	32:68	13.9:1		ap. stand.	low
		388	M	21	BC	8	2.35	84.6	3.29	0.238	0.015	0.15	96:40	13.7:1	+	ap. stand.	low
		376	F	19	C	10	4.25	78.9	3.34	0.254	0.053	2.12	61:39	13.1:1	3+	ap. stand.	ap. stand.
		450	F	18	*	4	3.02	87.9	3.22	0.257	0.026	0.89	78:22	12.5:1		low	low
		314	M	21	BS	2 11	2.42	100.1	2.84	0.230	0.027	0.53	84:16	12.3:1	±	high	high
	Streptococcus	364	F	17	BC	2	3.78	84.6	4.13	0.226	0.018	1.06	80:20	18.2:1	2+	+200	+200
		283	F	19	BS	4 3	2.65	83.4	3.29	0.261	0.018	0.46	88:12	12.7:1	+	+200	+100
		163	F	21	DR	7 10	7.01	82.4	2.04	0.241	0.493	5.53	27:73	8.4:1		+1200	+1200
		332	F	21	D	3 4	2.33	94.0	2.13	0.261	0.008	0.95	69:31	8.2:1		±100	−40

Miscellaneous

Sheep amboceptor; *B. abortus*	Donkey No. 4	M	18	C	8	4.06	78.2	2.36	0.179	0.005	2.60	48:52	13.1:1	6+		
Parasitic infestation	378	M	2	D		2.64	114.9	1.98	0.239	0.010	1.37	59:41	8.3:1	4+		

* B = bled out; S = shot; C = chloroformed; D = died; DR = ruptured liver; No. 448, chloral hydrate, and No. 450, magnesium sulfate intravenously.

† The amount of fat in the liver, as indicated by staining sections with scharlach R, is arbitrarily designated as: ± within normal limits; + slight increase; 2 + moderate; 3 + marked; 4+, 5+, 6+ very marked.

‡ Previous immunization: No. 294, 2 years 2 months, tetanus, pneumococcus, meningococcus; had been resting 10 months when sacrificed.
" " No. 363, 1 year 3 months, meningococcus, tetanus; had been resting 4 months when sacrificed.

§ Immunization discontinued after 4 and 16 days respectively. Condition complicated by infectious anemia.

** Died of acute toxemia.

a low value with most of the horses; the few exceptions account for the wide range recorded. The neutral fats in the non-immunized and resting horses were uniform in amount and indicate a low level under conditions approximating the normal; with the immunized horses the range was much higher.

The data obtained from the analyses of these livers of non-immunized and immunized horses indicate ratios between the phospholipids and neutral fats higher than those reported by Theis or MacLean. These percentage ratios are recorded in Table II. Owing to its lower phospholipid and higher free-cholesterol content, the phospholipid: free-cholesterol ratio of liver tissue from immunized horses, with the exception of those that died during a rest period, was lower than that of liver tissue from non-immunized horses. The phospholipid:free-cholesterol ratio seems to have a definite relation to the extent of the injury resulting from immunization with bacterial toxins.

The titers of the serums are included in the table to complete the record. The antitoxic titers are expressed in standard units. The potency of the antimeningococcus and antipneumococcus serums is expressed in relation to the New York State minimum control serum as Approximately Standard, Low, or High. The antistreptococcus serum is classified with the antimeningococcus and antipneumococcus serums because it is produced by immunization with living cultures, but the titer is expressed in standard antitoxic units. The procedure of immunization, with the exception of the diphtheria horses which were experimental, follows closely that prescribed in the Standard Methods of the Division of Laboratories and Research of the New York State Department of Health.[13]

At autopsy the tissues of the organs were prepared for microscopic examination to determine the character and extent of the degenerative changes. These varied greatly but were most marked in the liver, kidney and adrenal glands. Apart from slight changes attributed to age, previous treatment, or artifacts of fixation, the livers of the non-immunized and resting horses were considered to approximate normal; the parenchyma to be quite so. The chemical analyses gave a uniform ratio approximating the average of 19.8 : 1 between the phospholipids and the free cholesterol. In so far as practical, therefore, these horses afforded a basis for comparison with the changes that were observed in the other groups of immunized horses, which had varying degrees of parenchymatous degenerative change.

In some instances this appeared to be more marked in the kidney than in the liver, but in others, and especially in horses with ruptured livers, the reverse was true. Areas of hemorrhagic extravasation were especially marked in these livers.

The most advanced and extensive lesions in the liver were found in the horses that died with rupture of the liver. Less than 10 per cent of the cells retained any of their structure in horse No. 163; in No. 325 the nuclei, cytoplasmic reticulum and granular elements had disappeared and were replaced with hyaline material stained faintly. In others the cytoplasm had degenerated in a similar manner, but the nuclei had survived. The parenchymatous degeneration affected the liver cells quite generally. Fatty infiltration, varying in degree throughout the liver, appeared in zones of the lobule or in areas. There were foci of degeneration and necrosis infiltrated with round cells, resembling the focal necrosis observed in typhoid fever. Also, changes suggesting early stages of cirrhosis were noted occasionally. The degenerative changes in the liver cells affected the periphery first and the basal portion and the nucleus last. The outer third or two-thirds of the cell may separate, forming threads which, when stained with hematoxylin and eosin, resemble the amyloid liver but do not take the characteristic stains until the advanced stages are reached. The amyloid thus appears in this hyaline material. The extremes of early toxic degeneration following a single fatal dose of diphtheria toxin and of late amyloid change are recorded respectively in the photomicrographs of horses Nos. 380 (Figs. 3 and 4) and 163 (Figs. 8 and 9). In some instances the hyaline material is derived from the blood following stasis and degeneration.

Owing to the fact that these horses had been under immunization for varying periods of time and with varying quantities of toxic material, it is only possible in this series to note the fact that the most pronounced and most advanced changes in the liver were found in those horses with the lowest ratio of phospholipids : free cholesterol.

The ratio of phospholipids: neutral fat varies quite markedly in the different groups of immunized horses. The ratio of phospholipids: free cholesterol was practically uniform in the non-immunized and resting horses. In these two groups this ratio corresponded closely, whereas among the animals under active immunization the phospholipids were reduced, and the phospholipid : free-cholesterol ratio, in general, corresponded with the changes in the liver; the reduction

in this ratio was most marked in the 5 horses that had ruptured livers.

Finally, a striking variation was noted in the esterified cholesterol. This was greatly increased in horse No. 163, which had been immunized for more than 7 years with streptococcus and died of a ruptured liver. The blood serum had consistently a very high antitoxic titer (1200 units per cc.).

Frozen sections of some of the livers which had been hardened in formalin were stained with scharlach R. The results are recorded in Table II to indicate, in general, the amount of fat observed with this stain. The disposition of fat in the liver cells of these immunized horses was interesting in that there appeared to be stages of the degenerative process in which fat globules within the cell accumulated, increasing in size. In later stages they were not so apparent, yet the fatty substance had increased, as shown by chemical analyses and by the scharlach R stain.

Correlation of the changes in the liver tissue of the immunized horse with the results of the chemical analysis is complicated by the protective action of the immunization which was, in varying degree, adequate or inadequate. This, however, is undoubtedly what occurs in the course of prolonged human infections in which the liver is involved. In a few instances an early stage of cirrhosis appeared to be associated with, or to follow, degeneration, necrobiosis and necrosis of the parenchyma. Although the cells throughout the liver suffered quite generally, the character and extent of the parenchymatous degeneration varied greatly in the different horses. The liver cells were protected as a result of the prolonged immunization. Despite extensive injury and even necrosis, many cells survived, and the nucleus appeared to be less vulnerable than the cytoplasm.

Summary

Analytical data are recorded indicating the distribution of the lipids in the livers of 6 non-immunized, 2 resting, and 41 immunized horses: 11 with tetanus toxin; 6, diphtheria toxin; 1, botulinus toxin; 7, meningococcus cultures; 12, pneumococcus cultures; and 4 with combinations of streptococcus cultures and toxin.

The degenerative changes that developed in the liver as a result of the immunization are described and are recorded in the photomicrographs.

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DESCRIPTION OF PLATES

PLATE 59

FIG. 1. Horse No. 435. Female, 23 years, weight 950 pounds. Not immunized; bled (7000 cc.) twice; received one dose of 2000 units of tetanus antitoxin. January 1933, bled out (15,500 cc.) and shot. Liver weighed 5920 gm.

Section stained with hematoxylin and phloxine shows approximately normal liver. × 150.

FIG. 2. Horse No. 385. Female, 16 years, weight 1150 pounds. Immunized with tetanus toxin 10 months, doses of 0.7 to 350 cc., the maximum, given at intervals of 4 to 8 days the last 3 months. Oct. 28, 1932, prolapse of rectum; sacrificed by bleeding out.

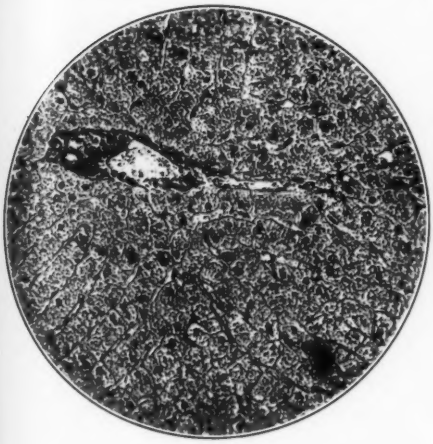
Autopsy: General condition good, medium fat; thrombosis of branch mesenteric artery; large and small intestine thickened, edematous with hemorrhagic areas; subendocardial hemorrhages in left ventricular valve; liver weighed 6400 gm.

Section stained with hematoxylin and phloxine shows degenerative change of moderate degree. × 150.

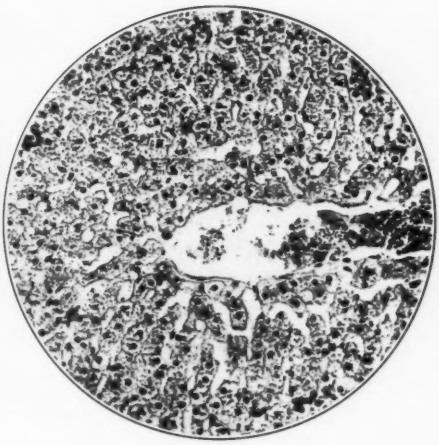
FIG. 3. Horse No. 380. Male, 2 years, weight 525 pounds. Dec. 14, 1933, received tetanus antitoxin and 6 cc. of diphtheria toxin diluted 1:20 (150 MLD) subcutaneously, followed by swelling of both sides and along abdomen. Dec. 28, 1933, found dead.

Autopsy: Petechiae in small intestine, pleura, and pericardium; congestion and edema of lungs; kidney and spleen somewhat congested; liver weighed 7075 gm.

Section stained with hematoxylin and phloxine shows the marked changes of an acute fatal toxemia in a young horse. × 150.



1



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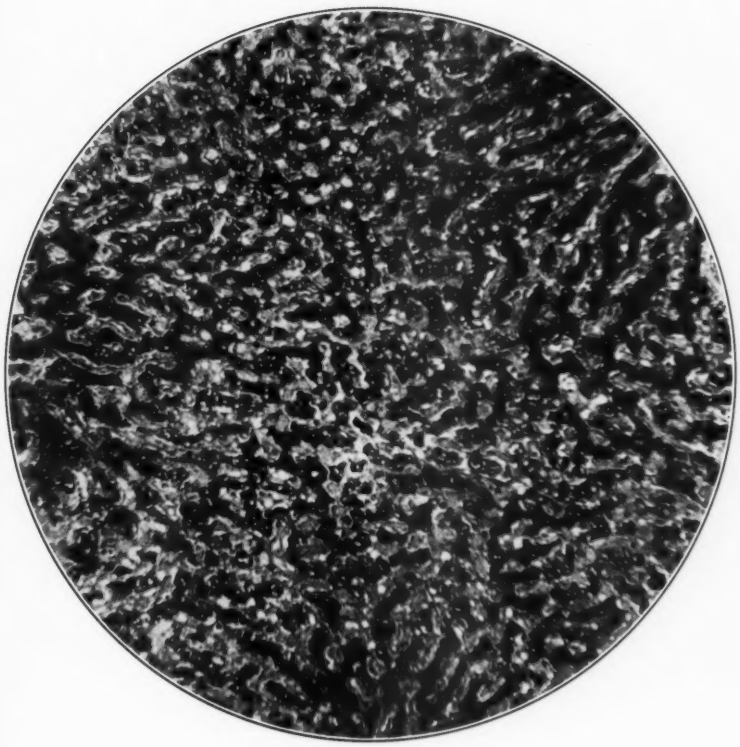


3

PLATE 60

FIG. 4. Higher magnification of Fig. 3. × 500.

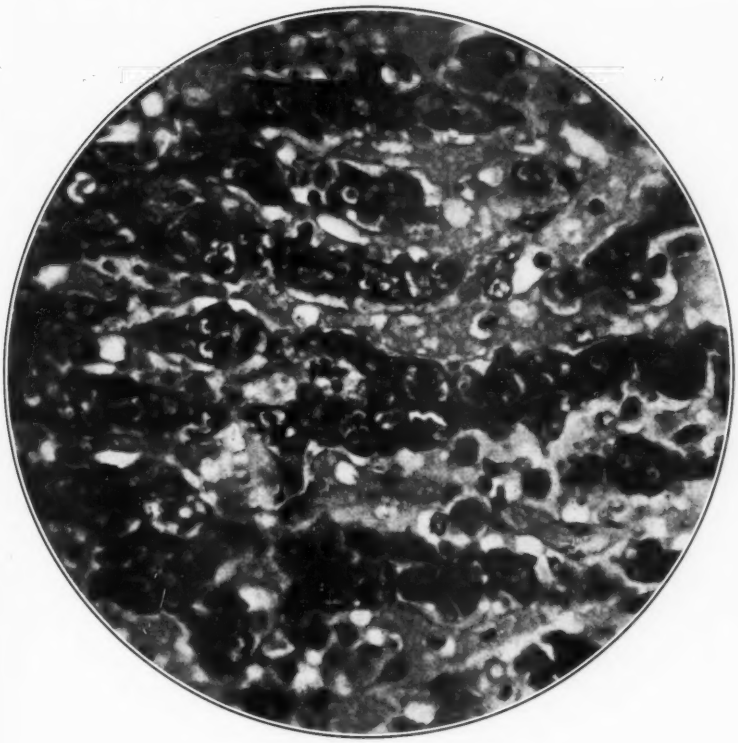
FIG. 5. Horse No. 451. Female, 21 years, weight 925 pounds. Immunized with pneumococcus type I (Neufeld strain) living cells for 6 months, with doses of 25 to 225 cc., a maximum, followed by four doses of whole culture containing 2 per cent blood, 100 cc. each. A month later, Nov. 6, 1933, shot.

Autopsy: Vegetative endocarditis, mitral and aortic valves; marked petechial eruption noted in various tissues and organs; liver, brownish yellow in appearance, weighed 7160 gm.

Section stained with hematoxylin and phloxine shows changes of more marked degree than those in Fig. 3. × 150.

FIG. 6. Horse No. 339. Male, 5 years, weight 777 pounds. Immunized with tetanus toxin 1 year and 4 months, doses of 0.7 to 200 cc., a maximum, given the last 12 months at intervals of 4 to 8 days. July 25, 1932, sacrificed by bleeding out under chloroform anesthesia owing to poor condition and low titer of the serum.

Section stained by hematoxylin and phloxine shows advanced degenerative processes with appearance of early stage of amyloid change which, however, does not stain in a characteristic manner with iodine and sulfuric acid, methyl violet or iodine green. × 150.



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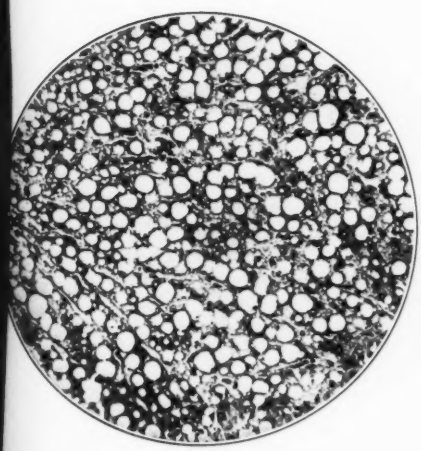
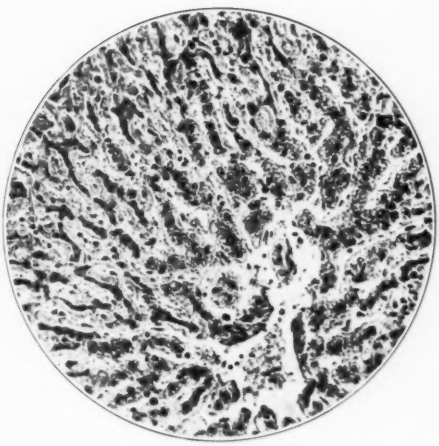


5



6

Wadsworth, Hyman and Nichols

Lipid Content of Livers of Horses

PLATE 61

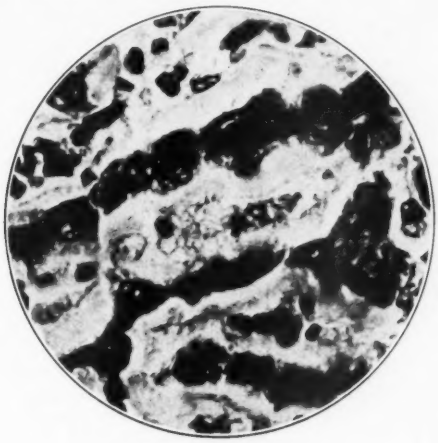
FIG. 7. Higher magnification of Fig. 6. × 500.

FIG. 8. Horse No. 163. Female, 21 years, weight 900 pounds. Immunized, beginning June 1924, with streptococcus (Dochez, N. Y. 5) living culture in agar for 12 months, then supplemented by toxin in doses of 10 to 525 cc., a maximum. Rested July 1926 to August 1927. Immunization resumed through June 1928; horse then rested until April 1930, when immunization was again commenced. May 6, 1932, 7 A.M., found dead.

Autopsy: 11: 30 A.M. Hemorrhage into abdominal cavity from large ruptures of the liver, margins and dorsal surface of right and middle lobes; liver tissue soft and light colored; marked degeneration throughout.

Section stained with hematoxylin and phloxine shows the most advanced degenerative processes observed. The hyaline material was practically all amyloid and stained a typical reddish violet with methyl violet. × 150.

FIG. 9. Higher magnification of Fig. 8. × 500.



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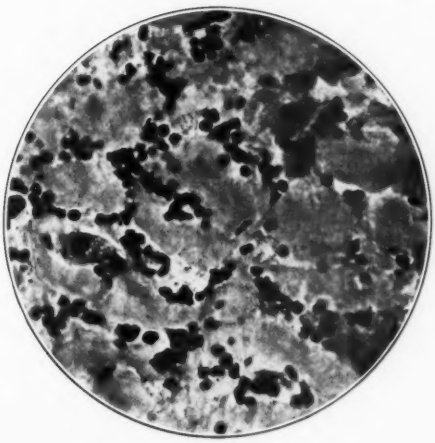

9

A GANGLIONEUROMA IN THE NECK OF A CHILD *

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Neoplasms of nervous origin are always interesting because of their comparative rarity, their doubtful origin, their variable structure, the difficulty of properly naming and classifying them, and the uncertainty of their clinical behavior. The particular tumor whose description follows was therefore welcomed and the result of its study made the starting point of a thorough literary and critical survey of the group of tumors to which it was finally assigned.

REPORT OF CASE

Clinical History: A. C., a white female, 7 years of age, whose parents are living and well, was delivered by a normal labor, weighing at birth 9½ pounds. She was breast fed for 1 month only.

The first teeth erupted at 3 months but the teeth of the first dentition were all poor in quality. Infancy and early childhood were uneventful, but at 5½ years of age, a swelling made its appearance in the region of the cervical lymph nodes and continued to enlarge until, her parents becoming apprehensive, she was brought to the hospital. She was thought to have tuberculous adenitis and was given a course of five X-ray treatments, 3 weeks after the last of which she was admitted to the Hahnemann Hospital on Feb, 16th, 1931.

On admission the patient was rather pale, though apparently well nourished. Examination showed the breathing to be slightly obstructed and the tonsils enlarged. A large, smooth, nodular mass was present in the right side of the neck which was not tender, and did not fluctuate. Blood examination on admission showed hemoglobin 70 per cent, erythrocytes 3,500,000, leukocytes 5900. A second blood examination made March 4th showed the hemoglobin to be 72 per cent, erythrocytes 4,290,000 and leukocytes 6200, of which 58 per cent were polymorphonuclears, 35 per cent lymphocytes, and 7 per cent transitionals. The temperature varied between 97 and 99.8° F., and the pulse between 76 and 118.

On Feb. 23rd, 1931, a tonsillectomy was performed and a pharyngeal abscess opened. The general condition then improved, though no change occurred in the swelling in the neck and the temperature continued to rise occasionally.

An examination of the chest made March 5, 1931, showed bronchial breathing, more tubular than usual, in the midportion posteriorly, with broncophony

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and well transmitted tactile fremitus and râles. Heart normal. A Mantoux test was performed on the right forearm and reported positive.

An X-ray examination of the chest made March 10, 1931, showed distinct thickening of the roots of the lungs with extension to both bases and to the right upper lobe. There were a few calcified areas at the roots of the lungs and some mottling of both upper lobes. The disturbance at the roots of the lungs was thought to be in the bronchial lymph nodes.

On March 12, 1931, another Mantoux and a von Pirquet test were performed on the left forearm, and on March 18th both were reported negative.

On April 4th the patient was released on the mother's request, and the diagnosis recorded as tuberculous adenitis.

She was readmitted to the hospital on April 23, 1932. Blood examination gave 7400 leukocytes, of which 61 per cent were polymorphonuclears, 38 per cent lymphocytes and 1 per cent basophiles. Two days later the hemoglobin was 91 per cent, leukocytes 6200, of which 82 per cent were polymorphonuclears, 13 per cent lymphocytes, 2 per cent transitionals and 3 per cent eosinophils. After two more days there were 65.5 per cent polymorphonuclears (55.5 per cent mature, 7 per cent immature and 3 per cent metaleukocytes), 28 per cent lymphocytes, 4.5 per cent transitionals, and 2 per cent eosinophils, with abundant platelets, many broken, poorly stained and degenerated white cells. The red cells were normal. The temperature, 100° F. on admission, descended to 99° F. that night, and remained at that point.

On April 27, 1932, an X-ray examination of the chest showed the conditions previously reported, except for pulsation in the right infraclavicular region thought to be characteristic of tuberculous infection.

On May 4, 1932, the patient was operated upon and a firm encapsulated tumor about the size of a lemon was removed from a position deep down in the neck. At the upper pole it appeared to be attached to some bony structure; elsewhere it was free.

Specimen from the operation consisted of two masses of tissue, one 6 by 5 by 4 cm., the other 5 by 3 by 2.5 cm., weighing 90 gm. They were white, fairly firm and easy to section, but the gross appearance was not characteristic of any recognized condition. There were no areas of caseation and no suggestion of tuberculosis.

After the operation the temperature of the patient varied about 100° F. for a week or so, then gradually descended to reach normal by May 20th. Additional X-ray treatments were given for prophylaxis against recurrence, on May 24th and May 27th, and the wound having healed the patient was discharged June 18th, 1932.

She reported at the hospital for follow-up examination June 24th, when she looked well and said that she felt well.

She was again seen on May 5th, 1934 (2 years later), and seemed to be quite well. Her mother, however, said that she coughed during the day and was nervous during the night. She also turned her head to one side when swallowing, probably because of the effect of the operation scar.

Careful examination of the scar and its neighborhood showed no evidence of any recurrence of the tumor. She has, however, a curious soft swelling, sharply limited to the left side of the tongue, thought by the mother to have developed after leaving the hospital. An X-ray examination of the chest showed no sign of metastatic tumors in the lungs.

Microscopic Examination

The tumor consists of a fibrillar background or stroma in which are scattered cells and cells in groups.

The fibers that make up the greater part of the tumor present considerable diversity of appearance. Some are extremely fine and wavy, others coarse and collagenous. The indistinct bundles of fibers intertwine so that they are always cut both longitudinally and transversely. Some have their respective fibrils widely separated, as in edema, others are compact. There is an occasional tendency to hyalinization, and at many points a granular breaking down followed by colliquation necrosis leading to the formation of minute indefinite spaces.

The nuclei of the fibrillar tissue are elongate, oval and vesicular where the fibers are coarse; elongate, slender and more uniform where they are fine and wavy. In many places distinct palisades of nuclei show indubitably that the fibers belong to nervous tissue. A few definite nerve fasciculi are seen, but may belong to antecedent nerves about which the tumor has grown. Except in them, no medullary sheaths were found.

The cells distributed through this background of fibers seem to form an ascending series that begins with small cells not unlike lymphocytes and ends in typical ganglionic nerve cells. The various forms — neurocytes, neuroblasts, sympathoblasts and ganglion cells — occur together. Individual cells in all or any of these stages of development are scattered singly or in groups throughout the whole tumor.

Small cell groups of spindle shape, and composed of a few large unmistakable nerve cells, with abundant cytoplasm, beautiful vesicular nuclei and large distinct nucleoli, flanked by smaller cells tapering off to very small ones at the ends of the spindle, not infrequently occur in the intervals between the fibers.

Larger collections of cells constitute a striking picture. A good many correspond with the ganglionic nerve cell groups characteristic of ganglioneuroma, and adjacent to them palisade arrangement of the nuclei shows the fibrillar tissue to consist of Schwann cells. There is no doubt but that the tumor is a ganglioneuroma. But it is not without its eccentricities. Many of the cells are immature forms closely or loosely massed together in a very delicate or loose stroma,

or in indefinite spaces in the stroma. These cell aggregations, so numerous, so large, and so indefinite, misled some of those who first examined the tissue into the error of believing that they were looking at some form of malignant epithelial tumor.

The cells represent all of the stages of development, but instead of each progressing regularly to the ganglion cell stage, those of all stages seem to multiply at random, then degenerate or liquify.

Scarcely a nerve cell, primitive or advanced in development, appears to be in a state of good health. Large ganglionic cells with beautiful vesicular nuclei commonly have finely or coarsely vacuolated cytoplasm, or they possess two, three or four nuclei, uniformly developed and healthy; or, one or several nuclei may appear normal while others may be mitotic, pyknotic or vacuolated. Mitoses, not frequent, may be found in the cells of the same group. In adjacent groups there may be none. Judging by this criterion the growth of the tumor should have been slow and should have progressed by multiplication of cells, now here, now there.

The retrogression and colliquation of the ganglion cells was attended by finer, then coarser vacuolation, then fraying at the edges. In some cases there was cytopyknosis and karyopyknosis in which the nuclei became small, dark colored bodies eccentrically situated toward the surface of the cell whose cytoplasm was solid, uniform and eosinophilic.

The general impression resulting from the study of sections stained by hematoxylin and eosin, iron hematoxylin, Weil's and Bielschowsky's methods may be summed up as follows. The neoplasm is a ganglioneuroma whose development began with the multiplication of embryonal neurocytes, and continued through the continued multiplication of those primitive cells and their evolving descendants up to the stage of ganglion cells. Whether perfected ganglion cells can multiply is uncertain, but many which seem to have reached perfection contain two, three and four nuclei and show an occasional mitotic figure. These ganglion cells probably give off neuraxons, which account for the nerve fibrils brought out by the Bielschowsky stain, and seem to excite the proliferation of the Schwann cells which show the palisades of nuclei. Then the ganglion cells, and many of the sympathoblasts not yet that far developed, lose their vitality, retrogress and dissolve into the jelly-like accumulations by which the collections of dying cells are surrounded. In a few

instances the dead cells calcify so that occasional, small, irregularly rounded aggregations of lime salts occur in the tissue. The generations of cells that have matured, produced fibrils and disappeared, account for the neurofibromatous stroma or matrix of the tumor.

Comment

Wahl [137] in speaking about ganglioneuroma in his excellent and complete paper credits its name "ganglioneuroma" to Odier [97] in 1803, its origin from sympathetic ganglia to Günsburg [59] in 1845, and its position with respect to other nervous tumors to Virchow in 1863. With the subsequent publications of Loretz,[84] Key,[8] and Weichselbaum [140] the tumor became a well established and generally recognized entity that has attracted more and more attention and led to the reporting of more and more cases with the passage of time, as shown in the papers of Wahl,[137] Hook,[66] Rapp,[110] Pick and Bielschowsky,[106] Dunn,[42] von Fischer,[46] Riggs and Good,[112] Smirnoff,[128] and Bigler and Hoyne.[20]

It is interesting to see that the number of reported cases increased from 33 in 1911, 36 in 1913, and 68 in 1932, to the present total of 143 that can be drawn from our bibliography. Accuracy regarding the number of published cases is impossible because of the difference of opinion as to just what tumors shall be included under the name ganglioneuroma. Ever since the tumor was first described by Odier the criterion for its identification seems to have been the presence of an abnormal number of ganglion nerve cells, but Gibberd [53] has described as ganglioneuromas two tumors in which no ganglion cells were found in the sections examined by Mr. R. Davies-Colley, his pathologist.

Pick and Bielschowsky [106] in 1911 expressed the opinion that the tumors of the group to which the ganglioneuromas belong, originate through embryonal malformations or the displacement of multipotential embryonal neurocytes, and consist of "ripe" or "unripe" neuroblasts. This idea agreed with that of Brossok [25] in 1911 and Dunn [42] in 1915, and was elaborately discussed, especially with reference to the benignancy and malignancy of the tumors by von Fischer [46] in 1922.

According to von Fischer the primitive nerve cells, or sympathogonia, as they multiply to form tumors may maintain their primi-

tive or original shape and indicate their nature solely by the formation of the finest fibrils which lie between the cells without any kind of definite arrangement. A tumor of this structure is called "sympathogonioma" by Kohler, and constitutes the most primitive variety of neuroblastoma. With a slightly more advanced stage of differentiation these fine fibrils are gathered into coils or skeins about which there is a more or less distinct arrangement of the sympathogonia to form rosettes, while elsewhere numbers of the cells are advancing in size and differentiation to sympathoblasts or the antecedents of the ganglion cells. A tumor of this slightly higher structure is called "sympathoblastoma." When the number of sympathoblasts begins to exceed the number of sympathogonia, and more definite ganglion cells appear, singly or in groups, amid bundles of fibers and cells of Schwann, the tumor becomes "ganglioneuroma simplex."

It thus appears that two entirely different appearing tumors, the sympathoblastoma (neurocytoma of Marchand [89] and Wright [142]) and the ganglioneuroma, simply represent the beginning and terminal stages in the neoplastic development of the embryonal nerve cells of which they are made up.

But the vegetation and differentiation of the cells do not regularly parallel one another. The cells may remain in the stage of sympathogonia or neuroblasts, when the tumors, purely cellular, highly malignant and metastatic, are easily mistaken for small round cell sarcomas; or some of them may persist in that primitive state while others differentiate into ganglion cells with nerve fiber and Schwann cell additions, giving rise to tumors, parts of which seem to be of one kind, other parts of another kind. Such a tumor was described by Robertson [116] as a ganglioneuroblastoma.

As the respective malignancy or benignancy of the nerve cell tumors is the result of the failure of the cells to mature on the one hand, and the perfection of their maturation on the other, any tumor containing sympathoblasts (or neurocytes) may be considered as malignant, or potentially malignant, in proportion to the number and vegetative activity of the primitive cells it contains. It is the small size of the primitive cells, their independence, and the ease with which they can be transported that are responsible for the metastases. It may therefore be assumed that every metastasis consists primarily of such primitive elements. But just as at the

primary seat of occurrence many of the cells progress in differentiation and some reach the final stage of ganglion cells, so in the metastases some or many of the cells may advance to complete differentiation and some or many ganglion cells be found in them. It may even be possible for all of the cells to complete the differentiation to ganglion cells incapable of multiplication so that an originally malignant tumor may become benign. Such a case was studied by Cushing and Wolbach.[38]

The tumors are further divided into *ganglioneuroma immaturum* and *ganglioneuroma imperfectum*. These names explain themselves.

It is interesting that the ganglion cells sometimes seem to retain the power of multiplication until complete specialization is attained. Many of the cells, whose appearance suggests maturity, may be found in mitosis, or to have two or many nuclei.

Ganglioneuromas of the central nervous system have their histological structure increased in complexity through the presence of neuroglia elements of all kinds and in all stages of development. These constitute a special group of tumors to which the name ganglioglioneuroma has been applied.

But most peripheral ganglioneuromas also contain neuroglia-like cells, Schwann cells and nerve fibers.

Age Incidence

Ganglioneuroma may occur at any age. Von Fischer [46] found one in a stillborn infant. The tumor studied by Clegg and Moore [33] was present when the child was born. It is frequently said to be a tumor of childhood, but of 98 cases with age data we find 33 to have been less than 10, and 64 more than 10 years of age. Five of the cases in our bibliography were beyond 60 years of age, *viz.* Guizetti [58] 57 years, Brüchanow [26] 65 years, Bianchi [18] 68 years, Uyeyama [134] 69 years, Friedrich [48] 73 years, and Weichselbaum [140] 79 years.

Sex Incidence

It is also said to occur more frequently in female than male patients, and for this there seems to be some reason, as in 99 cases with sex data 56 occurred in females and 43 in males.

Anatomical Distribution

The left side of the body was affected in 22 and the right side in 16 cases. Many of the tumors, especially the mediastinal and retroperitoneal, are without information as to the side of the body in which the tumor originated.

The anatomical distribution is so general that ganglioneuromas may be encountered almost anywhere. The cases referred to in our bibliography were distributed as follows:

I. ABDOMINAL

(1) Intestinal
- Poate and Inglis [107]

(2) Mesenteric
- Bland-Sutton [21]
- Goodhart [56]
- Jones [71]
- MacNaughton-Jones [87]
- Paterson [101]

(3) Pancreatic
- Bianchi [18]

(4) Pelvic
- Beneke [14]
- Chiari [32]
- Newmann [95]
- Pick [105]
- Schorr [125]
- Stoeckel [130]

(5) Renal
- Bigler and Hoyne [20]

(6) Retroperitoneal
- Babcock [9]
- Berner [17]
- Busse [29]
- Cappell [31]
- Chiari [32]
- Cripps and Williamson [37]
- Fabris [43]
- Falk [44]
- Fischera [47]
- Glockner [55]
- Heinrici [65]
- Hortolomei, *et al* [67]
- Jergesen [70]
- Kopřiwa [77]
- Krecke [79]
- McFarland [86]
- Miller [93]
- Oelsner [98]
- Ohse [99]
- Rapp [110]
- Rosenbach [118]
- Sato [120]
- Schleifstein [121]
- Soyka [131]
- Strada [133]
- Wegelin [139]

(7) Sacral
- Chiari [32]
- Günsburg [59]

(8) Suprarenal
- Bigler and Hoyne [20]
- Brüchanow [26]
- Buzni [30]
- Dalton [39]
- Dunn [42]
- Gamna [50]
- Geller [51]
- Hook [66]
- Jaffé [69]
- Oberndorfer [96]
- Peters [104]
- Ribbert [111]
- Schmidt [122]
- Wahl [137]
- Wassmund [138]
- Weichselbaum [140]

(9) Exact Site Not Known
- Arpino [6]
- Bartlett [11]
- Behan [12]
- Beneke (coeliac) [14]
- Roman and Arnold [117]
- Smirnoff [128]

II. CEPHALIC

(1) CEREBRAL AND CEREBELLAR

Achúcarro [1]
Arpino [6]
Berblinger [15]
Bielschowsky [19]
Cushing and Wolbach [38]
DeJong [72]
Dumas [40]
Katzenstein [74]
Lhermitte and Duclos [83]
Marinesco [91]
Olivecrona [100]
Pick and Bielschowsky [106]
Robertson [116]
Schmincke [124]
Uyeyama [134]

(2) CRANIAL NERVES AND GANGLIA

(a) Trigeminal

Benda [13]
Cooper [35]
Fabris [43]

(b) Gasserian

Günsburg [59]
Hackel [60]
Haenel [61]
Marchand [90]
Risel-Zwickau [114]

(c) Ocular

Krauss [78]
Perls [103]

III. CERVICAL

Benda [13]
DeQuervain [108]
Freund [49]
Friedrich [48]
Geymüller [52]
Glinski [54]
Harbitz [63]
Haven and Weil [64]
Loretz [84]
MacAuley [85]
Martius [92]
Riggs and Good [112]
Shirai [127]
Sommerfelt [129]
Stout [132]
Von Fischer [46]
Woods [143]

IV. FACIAL

Clegg and Moore [33]
Dunn [42]
Key [8]

V. PERIPHERAL

(1) FLANK

Wilmoth, Bertrand and Patel [141]

(2) KNEE

Hagenbach [62]

(3) SKIN

Kredel and Beneke [80]
Montgomery and O'Leary [96]

VI. MEDIASTINAL

Babcock [9]
Bergonzi [16]
Bigler and Hoyne [20]
Brunner [27]
Ranzi [109]
Rosenson [119]
Riggs and Good [112]
Scott and Palmer [126]
Von Rindfleisch [113]

VII. THORACIC

Borst [22]
Guizetti [55]

VIII. VASCULAR

Anschütz [7]
Jacobsthal [68]

From this summary of 127 cases it will be found that seventeen of the reported tumors were, like ours, situated in the neck. The case reports, accompanied by the necessary data, show eleven of the patients to have been children and four adults. The cervical tumor of earliest occurrence was in von Fischer's [46] case of a stillborn in-

fant; that of latest occurrence, Friedrich's [48] case in a woman aged 73 years. The average age of the affected children was 5 years, of the adults 40 years. Five of the tumors were said to have been on the left side, five on the right.

Our case, therefore, adds one more to the seventeen reported cervical ganglioneuromas, one more to the eleven tumors reported as occurring in children and one more to those occurring in the right side of the neck.

Single and Multiple Tumors

Ganglioneuromas usually occur singly, but may be multiple, and when so the tumors may be either in close relationship with one another, widely separated or generally distributed. In the case reported by Knobelauch [76] there was one tumor in the facial-auditory region at the anterior end of the body, and another in the sacral region at the posterior end. Other multiple tumors have been reported by Haven and Weil,[64] Henrici,[65] Kredel and Beneke,[80] Knauss,[75] Montgomery and O'Leary,[94] Roman and Arnold,[117] Risel-Zwickau,[114] and Soyka.[131] When there are many widely distributed tumors the condition is frequently spoken of as ganglioneuromatosis, and the distributed lesions may be systematic or symmetrical.

Systematic multiple ganglioneuromas to the number of eleven, all in connection with the cranial nerves were observed by Risel-Zwickau.[114]

Symmetrical multiple cases have been reported by Günsberg,[59] Clegg and Moore,[33] and by Kredel and Beneke,[80] whose patient had about 160 separate tumors, and Montgomery and O'Leary,[94] in whose case the skin of the patient was studded with cutaneous ganglioneuromas on the trunk and extremities, while the vermiform appendix removed at operation showed increase of ganglion cells. The patient studied by Knauss [75] had about sixty subcutaneous ganglioneuromatous nodules scattered over the trunk and thigh. Lhermitte and Duclos [83] observed a case with multiple larger tumors whose occurrence, preceded by pigmentation of the skin, seemed more like von Recklinghausen's disease than ganglioneuromatosis and raises interesting questions as to the relation between neurofibromatosis and ganglioneuromatosis, a matter beyond the scope of this paper.

Ganglioneuromas also sometimes occur in association with tumors of other kinds. Thus Hackel [60] observed one associated with meningioma, and Bianchi [18] one intimately associated with carcinoma of the pancreas.

Gross Appearances

The physical qualities and gross appearances of ganglioneuromas are not sufficiently characteristic to enable the diagnosis to be made without the aid of the microscope. They are of all sizes up to that of a human head. They are usually rounded, nodular, more or less definitely encapsulated, sometimes firmer, sometimes softer. Cystic ganglioneuromas have been reported by Kopřiwa [77] and Poate and Inglis.[107]

The primitive types are softer and more uniform because of the greater proportion of cells, the mature forms more fibrillar because of fiber formation by both nerve cells and Schwann cells, and the associated formation of reticulum and collagen bundles. The cut surface usually presents a distinct fasciculation. There may also be porosity which results from the degeneration of whole groups of the ganglion cells, sometimes before, sometimes after their maturation.

Prognosis

The prognosis can be made only through microscopic examination, and even with its aid it is difficult to foretell what will happen. Judgment must be based upon the developmental stages attained by the majority of the cells found. The more primitive and embryonal the cells, the more malignant the tumor; the more differentiated they are, the more benign. Unfortunately, as has already been pointed out, the same tumor may show both primitive and perfected types of structure, as in Case 2 of Beneke,[14] the cases of Dunn [42] and Martius.[92] Such cases must be looked upon with suspicion.

Malignancy, or what has been described as malignancy, is usually shown by metastasis. Cases with metastases have been reported by Beneke,[14] Berner,[17] Bianchi,[18] Brossok,[25] Busse,[29] Chiari,[32] Jacobsthal,[68] Miller,[93] Pick,[105] and Wahl.[137] The case reported by Key [8] is included by some critics, excluded by others.

In the case reported by Beneke [14] the tumor was made up chiefly of embryonal cells and the metastases, also composed of very small cells, were in the lymph nodes and vena cava. Metastases to the liver were found by Jacobsthal [68] and Wahl [137]; to the kidneys by Wahl [137] and Pick,[105] who also observed one on the surface of the diaphragm. There seem to be no cases of metastases to the lungs.

As the tumors seem frequently to be of multicentric origin and systematic distribution, a certain amount of caution must be exerted in judging whether multiple tumors result from metastasis. For example, the multiple tumors of the skin reported by Montgomery and O'Leary [94] can no more be thought of as metastatic than those of von Recklinghausen's disease.

Treatment

The literature seems to make no mention of recurrent ganglioneuromas. Most of the patients whose tumors were accessible and surgically removed seem to have been cured. Failures resulted when unexpected complications arose. There is no evidence that treatment by X-ray or radium is of value.

Summary and Conclusions

The tumor described is a well characterized ganglioneuroma. In it, however, nerve cells of all stages of development from neuroblasts to ganglion cells occur, and among them is a stroma made up of Schwann cells and nerve fibers.

It occurred in the neck of a little girl, and seems to be the twelfth case of its kind to be placed on record.

Three years after operative removal the patient is living, with no return of the tumor and no metastases.

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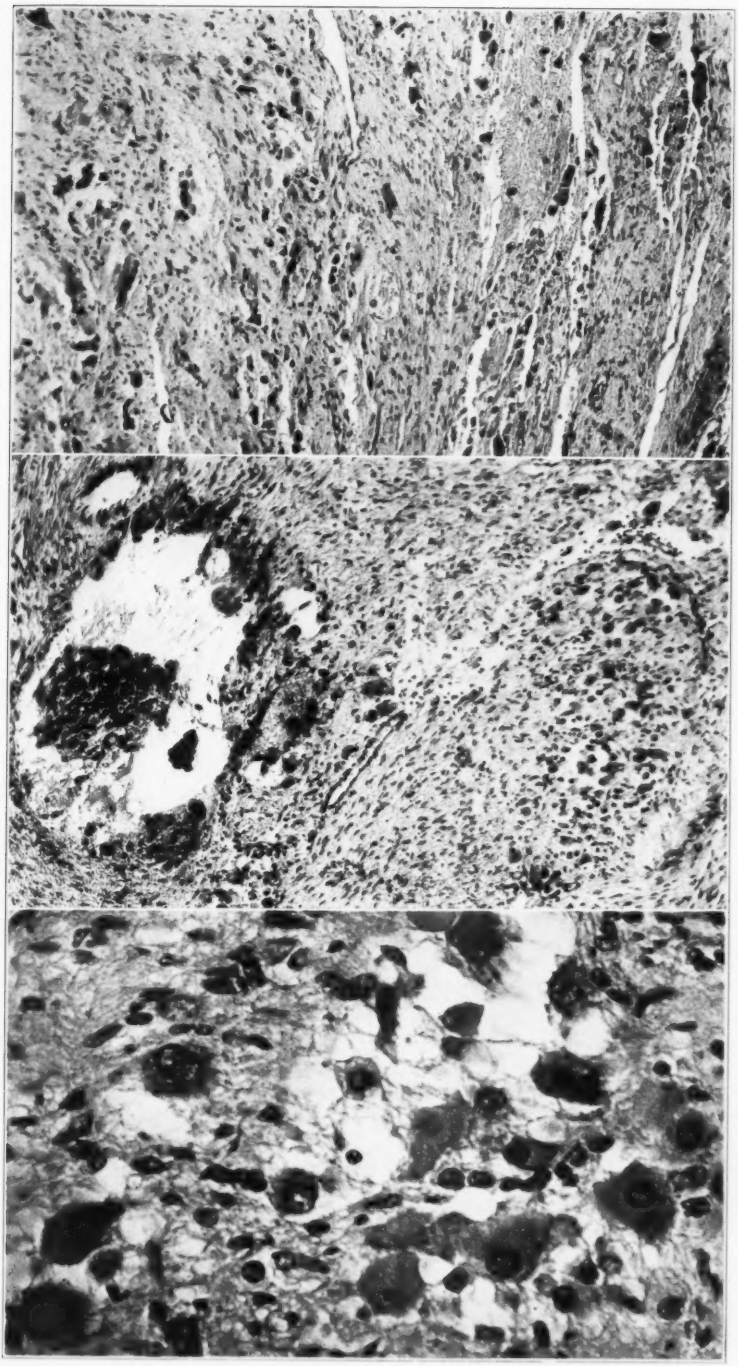
DESCRIPTION OF PLATE

PLATE 62

FIG. 1. Low power view of the general structure of the tumor with the neurofibromatous background and scattered, small collections of nerve cells.

FIG. 2. A field showing a ganglion of normal appearance with adjacent nerve and Schwann fibers and cells at one side, with an overgrown, degenerating and calcifying mass of cells opposite.

FIG. 3. Nerve cells in various stages of development up to that of ganglion cells.



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PRIMARY CARCINOMA OF THE LUNG *

A PATHOLOGICAL STUDY

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INTRODUCTION

Primary carcinoma of the lung is exciting an ever increasing interest, both because of its alleged rising incidence and because of the improvement in surgical technique allowing the cure of this disease in its early stages. The purpose of this paper is to classify the pathological anatomy of 69 autopsied cases of lung carcinoma occurring at the Boston City Hospital from Jan. 1, 1900 to August 1, 1934. A classification based on the microscopic morphology has been utilized in an attempt to determine the malignant potentialities, incidence by age and sex, and peculiar characteristics of different types of these tumors. It is to be hoped that a more accurate diagnosis and prognosis may be made from histological study of biopsied or expectorated tissue from these carcinomas in the future.

In 1912 Adler [1] published an analysis of 374 cases which had been reported in the literature up to that time. Of recent years, and especially since 1920, the literature abounds with references and historical reviews. For an adequate discussion of the historical, anatomical, pathological and clinical aspects of this subject, the reader is referred to the works of Adler,[1] Pilcher and Brindley,[2] Barron,[3] Vinson,[4] Weller,[5] Brunn,[6] Brockbank [7] and, more recently, Fried,[8] Gillespie[9] and Hill.[10]

CLASSIFICATION

Little or no uniformity exists in the classification of primary lung carcinoma. Thus, older authors divided their cases into tumors arising from (*a*) the epithelium lining the bronchi, (*b*) the epithelial cells forming the mucous glands, and (*c*) the epithelium said to line the pulmonary alveoli (the air sacs). More recent investigators deprecate a histogenetic classification and utilize a histological stand-

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ard. Adler, in 1912, expressed the view that most lung carcinomas were bronchiogenic in origin, and more recently Fried has thoroughly reviewed the subject and concluded that all primary lung carcinomas originate from the lining mucous membrane of the bronchi. Certainly if non-bronchiogenic carcinomas exist they are of rare occurrence. A classification based on the gross pathology seems to lend little clarification to the subject.[11]

For the present study the histological classification used by Weller,[5] Rogers,[12] and in part by Fried,[8] and other recent writers, has been utilized. The pleomorphism so frequently mentioned in relation to these tumors was occasionally found but presented no serious barrier to classification. The 69 carcinomas of this series have been divided into three large groups, namely, (*a*) squamous cell carcinomas, (*b*) adenocarcinomas, and (*c*) undifferentiated carcinomas. These will be discussed more fully below.

Squamous Cell Carcinomas: These tumors consist of the typical large cells with large clear nuclei and prominent single nucleoli, arranged in a manner suggesting the squamous epithelium seen in patches in the lining of the bronchi. Forty-two per cent (29 cases) were of this type and constituted the largest single group. Twenty-eight per cent of these tumors showed the formation of epithelial "pearls." Metastases were usually of the "squamous" type and rarely showed cornification or "pearl" formation. In 55 per cent the primary tumor was located in the left lung and in 44 per cent in the right lung. Forty-four per cent were in the upper lobes, 38 per cent in the lower lobes and 18 per cent at the hilum. The lobes were involved with the following frequency: left upper 20 per cent, left lower 24 per cent, right upper 24 per cent, and right lower 14 per cent. Thirty-one per cent of the total number presented as a mass at the hilum and 61 per cent either involved or occluded a primary or secondary bronchus.

Grossly the primary tumors were single, indurated, gray or white solid masses in 75 per cent of cases. Cavitation occurred in 17 per cent. Multiple masses in one lung were found in 8 per cent. Areas of tumor necrosis were relatively infrequent.

Adenocarcinomas: These tumors are very difficult to classify. Among them are tumors which undoubtedly in the past have been classified as "alveolar cell" carcinomas because their histological structure resembles that of fetal lungs. They comprise 24 per cent

(17 cases) of the entire series. Composed for the most part of cuboidal or cylindrical cells arranged in acinar formation, their chief distinguishing feature appears to be the secretion of mucus and their resemblance to bronchial mucous glands. Fifty-three per cent showed definite secretory function and 47 per cent were functionless. These will be referred to henceforth as mucinous and non-mucinous adenocarcinomas.

The non-mucinous type occurred in 8 cases, 4 of which showed a papillary adenomatous arrangement, and in three of these latter tumors ciliated columnar cells were found resembling very closely the columnar cells lining the bronchial tree. The possibility of these cells being remnants of normal bronchi was considered, but the presence of ciliated cells in the metastases of two of these tumors and the similarity of the cells to adjacent, non-ciliated tumor cells tend to eliminate this possibility. The four remaining adenocarcinomas showed no distinguishing histological feature, except a slight tendency to assume a "squamous-like" structure where the alveoli were compressed. However, they were not true acanthomas. The resemblance of these tumors to fetal lungs is suggested but not striking, and in view of the cilia found in tumors not unlike these it is believed that they are less well differentiated bronchiogenic carcinomas.

The primary tumors in the non-mucinous adenocarcinomas occurred equally in the right and left lungs. Thirty-seven per cent occurred in the upper lobes, 37 per cent at the hilum, only 12 per cent were in the left lower lobe and none were in the right lower lobe. Twenty-five per cent were in the right upper lobe and 12 per cent in the left upper lobe. In 12 per cent, diffuse multiple masses involved the whole of the right lung. Primary bronchi were involved or occluded in 37 per cent of cases and were negative or not described in the postmortem descriptions of 63 per cent.

The mucinous type of adenocarcinoma has been described at length in the past and has been called variously carcinoma myxomatodes (Willert[13]), colloid carcinoma and gelatinous carcinoma. Their striking resemblance to bronchial mucous glands and the presence of a mucoid secretion within the alveoli serves to mark them as a characteristic lung carcinoma. They are composed of cuboidal and cylindrical cells and careful search will nearly always reveal scattered cells in secretory phases. Their structure is most frequently

that of a malignant adenoma, although true adenocarcinomas are not rare. Their metastases in the majority of instances show mucinous secretion. However, non-secreting metastases occur.

Mucinous adenocarcinomas occurred in 9 cases and in 44 per cent the primary tumors were located in the left lung and in 55 per cent, in the right lung. Fifty-five per cent occurred in the upper lobes, distributed as follows: left upper lobe 33 per cent, right upper lobe 22 per cent. Eleven per cent each occurred in the left lower, right middle and right lower lobes. In 11 per cent the tumor encircled the lower end of the trachea and right bronchus. In 55 per cent a large bronchus was involved or occluded, while in 45 per cent the bronchi were negative or not described.

In gross the adenocarcinomas appeared most frequently as gray, firm, scirrhous tumors with scattered areas of softer, yellowish tissue frequently showing grossly visible mucus. Necrosis was uncommon but when present occurred in the papillomatous carcinomas. In 94 per cent the primary tumors were a single mass occupying a lobe, the hilum or both.

Undifferentiated Carcinomas: This type is composed of the "small cell" tumors which in the past have frequently been called sarcomas. Barnard,[14] Maxwell,[15] and more recently Karsner and Saphir,[16] have shown that these tumors are in reality carcinomas. Karsner and Saphir conclude that they are carcinomas because of their cellular arrangement, absence of reticulum, vascularization, connective tissue relations, gross characteristics resembling obvious carcinomas and distribution of metastases. Barnard describes the microscopic picture as follows. "The cells are in the main oval and when cut transversely, round and have little cytoplasm. The nuclei are oval and the majority have a distinct chromatin net with chromatin nodes, but in others the whole nucleus is so deeply stained that the nuclear structure is obscured." These tumors have been called "oat cell," "oat seed cell," small cell, spindle cell and round cell tumors in the literature.

Thirty-three per cent of the carcinomas in this series were of this undifferentiated, small cell type. Fifty-six per cent occurred in the left lung and 43 per cent in the right. Only 43 per cent of these primary tumors could be localized by lobes and they were distributed as follows: left lower and left upper lobes 13 per cent each, right upper lobe 9 per cent, and right middle and lower lobes 4 per cent

each. In 9 per cent the entire left lung was infiltrated and in 4 per cent the entire right lung. In 22 per cent the primary tumor was at the hilum of the right lung and in 24 per cent at the hilum of the left lung. The primary tumor exhibited a mass at the hilum in 65 per cent of the cases. A secondary or primary bronchus was involved or occluded in 100 per cent. Complete occlusion occurred in 30 per cent. The primary bronchi were involved in over twice as many cases as in either of the other two types.

In gross these tumors varied from a soft, pink, sarcoma-like mass to hemorrhagic, necrotic and sometimes caseous masses. Hemorrhage and necrosis were prominent and infiltration of the tumors extended along the bronchial tree.

Summary of Classification

A brief description of the histological classification has been given.

Fifty-three and six-tenths per cent of all tumors occurred in the left lung and 46.4 per cent in the right lung. The primary tumors were distributed by lobes as follows: left upper lobe 18.8 per cent, left lower lobe 17.3 per cent, right upper lobe 18.8 per cent, right middle lobe 2.9 per cent, and right lower lobe 8.6 per cent. In 35.1 per cent the primary tumors were located at the hilum and in 4.3 per cent the entire lung was infiltrated from the hilum. The upper lobes and the hilum were the seat of the primary tumor in about an equal number of cases and together constituted the primary location in 72.7 per cent. The infrequency with which the right lower and middle lobes were involved is striking.

Either primary or secondary bronchi were involved or occluded in 68 per cent. In the remaining 32 per cent the bronchi were either negative or not described in relation to the primary tumor mass.

In gross the adenocarcinomas were indistinguishable from the squamous cell tumors unless mucoid secretion was visible. These tumors were usually single, indurated, gray or white masses, situated within the parenchyma of the lung, and involved the larger bronchi in less than one-half of the cases and the hilum in less than one-third. The undifferentiated tumors were soft, hemorrhagic, showed extensive areas of necrosis and, in the great majority of cases, infiltrated along the bronchial tree from a primary site at the hilum.

Incidence

General Incidence: Discussions of the increase in lung carcinoma are so voluminous and numerous that the subject cannot be done full justice here. That more lung carcinomas are being observed, both at autopsy and clinically, is undisputed. However, whether this is an absolute or a relative increase is undecided. Rosahn [17] summarized most of the available autopsy statistics in 1930 and found that lung carcinomas increased 102 per cent in the period from 1920–1928, as compared to the period from 1910–1919, while during these same periods carcinoma in general increased only 30 per cent. He cites this as proof of an absolute increase. Derischanoff [18] found both a relative and an absolute increase and Dissmann [19] believed there was an absolute increase in about the same periods. Sitsen [20] found no increase at Innsbruck. Lipschitz [21] in an analysis of postmortem statistics found an increase in lung carcinoma at Dresden and Zwickau and practically no increase at Copenhagen and Turin, and pointed out that these last two cities are much greater industrial centers than the first two. He believed the incidence of lung carcinoma to be closely related to the residence, vocation and environment of the population. These are only a few of the conflicting reports, and in conclusion it may be said that only when extensive international autopsy statistics, including both urban and rural populations, are available will the question be settled.

The incidence by 5 year periods is given in Table I. Rosahn [17] assembled these statistics at the Boston City Hospital from 1910–1928. Two lung carcinomas occurring between the years 1920 and 1924 have been added and Table I includes the entire period from 1900 to August 1, 1934.

Rosahn found that in the period 1925–1928 the percentage relation of all cases of carcinoma to total autopsies increased 20 per cent, while the percentage relation of primary lung carcinomas to all carcinomas rose 49 per cent, and concluded that this indicated an absolute increase in incidence. The figures previous to 1924 include so few primary lung carcinomas that they are worthy of consideration only in the aggregate. During this 25 year period the per cent of carcinomas occurring at autopsy rose from 6.12 per cent to 10.34 per cent (an increase of 68 per cent) and averaged 7.75 per cent. During this same period lung carcinoma increased in the per cent of

all autopsies but remained fairly constant at an average of 5.71 per cent of all carcinomas. Using these average figures for a basis, in the next 5 years the per cent of carcinoma rose from 7.75 per cent to 11.87 per cent (an increase of 53 per cent) while the per cent of lung carcinoma to all carcinomas increased from 5.71 per cent to 7.68 per cent (an increase of 34 per cent) or an actual decrease in incidence among all cases of carcinoma autopsied. In the subsequent period up to August 1, 1934, the number of cases of carcinoma autopsied decreased slightly from 11.87 per cent to 11.12 per cent (a decrease of 7 per cent) and the per cent of carcinoma of the lung

TABLE I

Incidence of Primary Carcinoma of the Lung at the Boston City Hospital

Year	No. of adult autopsies	Carcinomas		Primary lung carcinomas		
		Total	Autopsies	Total	Autopsies	All carcinomas
			per cent		*per cent*	*per cent*
1900–04	931	57	6.12	2	0.21	3.50
1905–09	865	52	6.01	4	0.46	7.69
1910–14	438	34	7.76	2	0.45	5.88
1915–19	526	45	8.55	2	0.38	4.44
1920–24	957	99	10.34	7	0.73	7.07
1925–29	1,532	182	11.87	14	0.91	7.68
1930–34* ...	2,624	293	11.16	38	1.44	12.96
Total	7,873	762	9.67	69	0.87	9.05

* To August 1, 1934

in relation to all carcinomas increased from 7.68 per cent to 12.96 per cent (an increase of 68 per cent). Thus, using comparable periods, there is an absolute increase only in the period from 1930 to August 1, 1934. When traced through single years, this rise has been fairly gradual while the per cent of autopsies revealing carcinoma has remained practically constant. The percentage relation of all cases of lung carcinoma to all carcinomas from 1929 to August 1, 1934 is as follows: 1929, 7.5 per cent; 1930, 10.5 per cent; 1931, 12.7 per cent; 1932, 14.2 per cent; 1933, 10.8 per cent; 1934, 19.1 per cent.

An explanation of this abrupt increase is difficult. However, the tremendous expansion of this hospital in recent years and the increased interest in pulmonary surgery has possibly allowed many

patients to remain in the hospital until autopsied, whereas formerly they were sent to institutions or homes for the care of incurables. No single carcinogenic factor was found at autopsy to explain this rise.

Incidence by Sex: Of the 69 cases examined, 79.7 per cent occurred in males and 20.3 per cent occurred in females, or in the ratio of 1 female to 4.5 males. This is in agreement with most of the statistics consulted. However, of the ten lung carcinomas occurring previous to 1920, five were in males and five in females, or in the ratio of 1:1. From 1920 to August 1, 1934, nine carcinomas

TABLE II

Distribution by Age of Primary Carcinoma of the Lung

Age incidence	Squamous cell carcinoma	Adenocarcinoma	Undifferentiated carcinoma	All tumors
years	*per cent*	*per cent*	*per cent*	*per cent*
20–29	0	12	0	2.9
30–39	10	6	9	8.7
40–49	13	23	17	17.3
50–59	34	23	48	36.2
60–69	20	23	17	20.3
70–79	20	6	4	11.5
80–89	0	6	4	2.9
	yrs.	*yrs.*	*yrs.*	*yrs.*
Youngest	36	29	31	29
Oldest	79	89	80	89
Average	57	53.1	53.8	53.7

occurred in females and fifty in males, or in the ratio of 1:5.5. European investigators have noted this increasing predominance of lung carcinoma in the male and have attempted to explain it on the greater exposure of males to war gasses, and industrial smoke and dust hazards, which probably exerted their irritating influences previous to 1920. It will be interesting to note if the influx of women into industry since the war will result in an increased incidence of lung carcinoma in the female.

Incidence by Age: Brunn [6] found that 62 per cent of 576 cases of lung carcinoma occurred in patients between 40 and 60 years of age. Weller [5] found the most frequent age was in the 6th and 7th decades, although rarer cases occurred at the extremes of life. Adler [1] noted

that the 6th decade was the most common period in which patients died of lung carcinoma. In general, the age incidence of carcinoma of the lung coincides with that of all carcinoma.

In Table II the age incidence is given by decades. Thirty-six and two-tenths per cent of all lung carcinomas occurred in the 6th decade and 73.8 per cent occurred in the 5th, 6th and 7th decades. Squamous cell and undifferentiated carcinomas occurred in these same periods. However, adenocarcinomas tended to be slightly more diffusely distributed.

Both the oldest and youngest cases occurred in the adenocarcinomatous group. Ewing [22] mentions an adenocarcinoma occurring in a girl aged 18. Pekelis [23] observed 5 cases occurring between the ages of 37–38 and 4 of these were of the adenocarcinomatous type. It would seem that lung carcinoma occurring in the younger age groups is more likely to be of the adenocarcinomatous variety.

Metastasis

Weller [5] states that carcinoma of the lung rarely fails to produce metastases. According to Klotz,[24] Adler,[1] Rogers [12] and Brunn,[6] metastases occur most commonly in the regional nodes and involve the liver, skeleton, brain, kidneys, adrenals and pancreas in approximately the order named. Metastases have been recorded in practically every portion of the body. No authors have tabulated metastases of a large series of cases according to the histological structure of the tumors. Also, direct extensions are mentioned so casually that it is doubtful if these have been carefully separated from metastases.

In the present series the body was examined in 67 cases and percentages of somatic metastases have been calculated on this basis in Table III. In 22 cases the head was examined and the intracranial metastases are discussed in a separate table. The tumors have been divided into the three groups mentioned previously and further subdivision is made where it is significant.

Squamous Cell Carcinomas: Twenty-seven cases in this group were examined and of this number 11 per cent failed to metastasize and 18 per cent produced secondary tumors only in the regional nodes.

A separate tabulation of primary tumors with and without cornification was made. Metastases occurred in twenty-one locations from tumors showing cornification and in twenty-four locations from those without cornification. Correlation by per cent of organs involved revealed no significant differences between these groups and it is suggested that these types have approximately the same metastatic potentialities. The presence of epithelial "pearls" and cornification possibly signifies a longer duration of the primary tumor.

Considering the entire group, metastases were most frequently found in the regional nodes. The liver, adrenals, kidneys, pleura, mesenteric nodes, heart and opposite lung were involved in that order of frequency. Rarer metastases occurred as tabulated in Table III.

Adenocarcinomas: Seventeen cases in this group were examined for metastases. Twelve per cent showed no metastases, 6 per cent metastasized only to the regional nodes and 88 per cent metastasized to twenty-two locations.

A tabulation of these tumors based on the presence of mucus revealed that all mucinous carcinomas showed metastases and in no instance were they confined to the regional nodes, while of the non-mucinous carcinomas only 75 per cent metastasized and in 12 per cent only the regional nodes were involved. The liver was involved in 44 per cent of the mucinous type and in only 12 per cent of the non-mucinous. The vertebrae were involved with the same relative frequency. It is concluded that non-mucinous carcinomas are less prone to metastasize than those with mucous secretion.

The adenocarcinomas exhibited a slightly less vigorous tendency to metastasize than the squamous cell tumors. Metastases occurred most frequently in the regional nodes, vertebrae, adrenals and mesenteric nodes in that order. Rarer metastases have been tabulated. The frequency with which bone is involved will be discussed under skeletal metastases.

Undifferentiated Carcinomas: Twenty-three cases in this group were examined and 96 per cent of these tumors showed metastases to thirty-five locations and 4 per cent showed involvement of the regional nodes alone.

These tumors exhibited the most vigorous metastatic powers of any group and spread widely outside of the thorax. Metastases

TABLE III

Distribution of Metastases in Primary Carcinoma of the Lung

Location	Squamous cell carcinoma	Adeno-carcinoma	Undifferen-tiated carcinoma	All tumors
	per cent	*per cent*	*per cent*	*per cent*
Peribronchial nodes	59	52	69	61.1
Liver	33	29	43	35.8
Tracheal nodes	18	23	24	25.3
Adrenals	33	17	21	25.3
Vertebrae	7	29	28	20.8
Kidneys	30	6	16	19.6
Retroperitoneal nodes	7	6	39	17.9
Mesenteric nodes	22	17	21	17.9
Cervical nodes	11	12	16	13.4
Opposite lung	14	12	4	10.4
Mediastinal nodes	0	0	16	10.4
Stomach	11	6	8	9.1
Heart	18	0	4	9.1
Pancreas	0	6	21	9.1
Iliac nodes	11	0	8	7.4
Ribs	11	12	0	7.4
Left pleura	14	0	0	5.9
Right pleura	11	6	0	5.9
Axillary nodes	0	6	12	5.9
Skin	4	6	8	5.9
Ileum	7	0	4	4.4
Spleen	4	0	8	4.4
Terminal phalanges	0	0	8	2.9
Spinal meninges	0	0	8	2.9
Uterus	4	6	0	2.9
Cecum	0	0	8	2.9
Esophagus	0	6	4	2.9
Femur	0	6	4	2.9
Diaphragm	7	0	0	2.9
Clavicle	0	6	0	1.5
Peritoneum	0	0	4	1.5
Jejunum	0	0	4	1.5
Tibia	0	0	4	1.5
Ilium	0	0	4	1.5
Appendix	0	0	4	1.5
Inguinal nodes	4	0	0	1.5
Gall-bladder	0	0	4	1.5
Psoas muscle	4	0	0	1.5
Testes	4	0	0	1.5
Ureter	4	0	0	1.5
Ovary	0	6	0	1.5
Broad ligament	0	6	0	1.5
Inferior vena cava	4	0	0	1.5
Pericardium	0	0	4	1.5
Radius	0	0	4	1.5

have been tabulated in Table III and it is of special interest to note that in 8 per cent there were extradural metastases in the spinal canal with compression of the cord. In an additional 8 per cent the terminal phalanges were involved. These odd metastases indicate the tendencies of this group to grow into blood vessels and produce secondary tumors which closely resemble sarcomas when biopsied.

Skeletal Metastases: Secondary tumors occurred in bone in 28.3 per cent of cases. Of these tumors involving bone, 31 per cent were adenocarcinomas, 42 per cent undifferentiated and 26 per cent squamous cell carcinomas. Fifty-five per cent of all mucinous adeno-

TABLE IV

Intracranial Metastases of Primary Carcinoma of the Lung

	Squamous cell carcinoma	Adeno-carcinoma	Undifferen-tiated carcinoma	Total
	per cent	*per cent*	*per cent*	*per cent*
Cerebrum	22	33	28	22.7
Cerebellum	22	0	28	18.1
Dura	11	0	0	4.5
Pons	11	0	0	4.5
Pituitary	11	0	0	4.5

carcinomas metastasized to bone and only 12 per cent of the non-mucinous type. The relatively high frequency with which adeno-carcinomas, and especially the mucinous type, involve bone is striking.

In all, 19 cases showed metastases with involvement of the vertebrae in 56 per cent, ribs in 21 per cent, skull, femur, terminal phalanges in 8 per cent each, and ilium, tibia and clavicle in 4 per cent each.

Routine examination of the lumbar spine and ribs was made in the majority of instances. However, other portions of the skeleton were not examined unless superficial examination aroused suspicion. Of necessity, these figures are incomplete.

Intracranial Metastases: The intracranial contents were examined in 22 cases and metastases were found in 36.3 per cent. Metastases were found with the following frequency: 44 per cent of 9 squamous cell carcinomas, 33 per cent of 6 adenocarcinomas, and 28 per cent of 7 undifferentiated carcinomas.

Table IV demonstrates that the cerebrum and cerebellum are the most frequent sites of metastases. The frequency with which secondary growths from primary lung carcinoma occur in the cranial cavity has been stressed repeatedly. Fried [8] found that 31 per cent of 47 cases metastasized intracranially and in many instances they were operated upon for primary intracranial tumors, and he emphasized the importance of eliminating the possibility of metastatic tumor of the lungs in all cases of suspected intracranial newgrowths.

Summary of Metastases

Somatic metastases occurred in 92 per cent of 67 primary lung carcinomas examined and involved forty-five locations. The regional-nodes, liver, adrenals, vertebrae, kidneys, retroperitoneal nodes, mesenteric nodes and cervical nodes, opposite lung, mediastinal nodes and stomach are the sites most frequently involved and the frequency is in the order named. Rarer metastases were numerous and widespread, as has been enumerated.

Skeletal metastases occurred in 28.3 per cent.

Cerebral metastases occurred in 36.3 per cent of 22 cases examined.

The undifferentiated, small cell type showed the most vigorous tendency to metastasize and the squamous cell, mucinous and non-mucinous adenocarcinomas follow in the order named.

From a study of metastatic lesions it seems evident that these tumors metastasize most frequently by the lymph channels, and commonly by the blood stream. No positive proof of metastasis by the air passages was found.

Extensions

Direct tumor extension involving vital structures is frequently mentioned in the literature. The heart and pericardium have been mentioned as direct sites of extension. A few instances of direct proliferation to the superior vena cava or to the regional nerves with resulting pain or dysphagia have been noted. For the most part, however, it is difficult to separate metastases from extensions in the larger series in which anatomical studies have been made. In the present series a careful attempt has been made to separate these two manifestations of malignancy and they will be discussed below according to the types of tumors.

Squamous Cell Carcinomas: In 27 cases examined 55 per cent of primary tumors showed direct regional extension. In 14 per cent there were extensions without metastases. Cornifying primary tumors extended in 50 per cent and non-cornifying in 57 per cent. Structures involved were the mediastinum, pericardium, heart, aorta, right pleura, left pleura, esophagus, diaphragm and ribs. In 1 case the superior vena cava was invaded with thrombosis of that vessel. In another case the primary tumor directly proliferated

TABLE V

Distribution of Extensions in Primary Carcinoma of the Lung

Location	Squamous cell carcinoma	Adeno-carcinoma	Undifferen-tiated carcinoma	All tumors
	per cent	*per cent*	*per cent*	*per cent*
Mediastinum	33	17	52	35.8
Pericardium	30	11	39	28.3
Aorta	18	6	23	17.7
Left pleura	11	0	34	16.4
Heart	18	0	17	13.4
Right pleura	14	11	8	11.9
Esophagus	11	0	17	10.4
Ribs	7	17	4	8.9
Diaphragm	11	6	8	8.9
Superior vena cava	4	11	4	7.4
Cervical region	4	6	0	2.9
Liver	4	0	0	1.5
Adrenal	4	0	0	1.5
Opposite lung	0	0	4	1.5
Skin	4	0	0	1.5
Spinal meninges	0	0	4	1.5
Clavicle	0	0	4	1.5

through the diaphragm and involved the liver and right adrenal. In another case the cervical region and skin were directly invaded.

Adenocarcinomas: In 17 cases examined 46 per cent extended from the primary site. In no instances were extensions present without metastases. Fifty-five per cent of the mucinous type extended locally and 37 per cent of the non-mucinous. Structures involved were the mediastinum, ribs, right pleura, superior vena cava, left pleura, diaphragm and cervical region. In 2 cases there was thrombosis of the superior vena cava as a result of tumor extension.

Undifferentiated Carcinomas: Of the 23 cases examined in this group 65 per cent involved the mediastinum or thoracic structures.

In 4 per cent there was extension without metastases. Extensions have been tabulated in Table V. Of special interest is one tumor which extended posteriorly between the ribs and compressed the spinal cord at the level of the fifth thoracic vertebra. In another instance the superior vena was thrombosed as a result of tumor extension.

Summary of Extensions

Of 67 cases examined 56.7 per cent showed extensions. In 6 per cent there were extensions without metastases. Sixty-five per cent of undifferentiated carcinomas, 55 per cent of squamous cell tumors and 46 per cent of all adenocarcinomas, extended locally. Only 37 per cent of non-mucinous adenocarcinomas extended locally. The percentage with which various structures were involved has been tabulated. Thrombosis of the superior vena cava occurred in 4 cases and in 2 cases the tumors extended to the cervical region and in 1 case the spinal canal was invaded with compression of the spinal cord.

Undifferentiated carcinomas exhibited the most marked tendency to extend locally and squamous cell, mucinous and non-mucinous carcinoma follow in the order named.

Associated Pathological Findings

Evidence of associated pulmonary inflammatory conditions were found in 58.8 per cent of cases. Either an active or organizing bronchopneumonia was present in 27.8 per cent; bronchiectasis, usually with small bronchiectatic abscesses, was found in 17.6 per cent. Four and four-tenths per cent showed lobar pneumonia, and fibrinous pleuritis and pneumoconiosis were present in 1.5 per cent each.

Complete atelectasis of a lobe or a lung occurred in 20.5 per cent and pulmonary infarction in 4.4 per cent. These conditions may be interpreted as the result of the mechanical occlusion of a bronchus or ramification of the pulmonary artery by direct tumor proliferation.

Chronic inflammatory disease of the lungs has frequently been accused of producing a predisposition to pulmonary cancer. It is believed that the repeated destruction of the epithelial cells lining

the bronchi leads ultimately to metaplasia and the production of atypical cells and these are thought to be pre-malignant. However, the great frequency with which the primary tumors are located at the hilum or in the upper lobes (72.7 per cent), and the frequency with which bronchiectasis, pulmonary abscesses and chronic pneumonia involve the lower lobes appears to preclude the presumption that these latter processes are sources of chronic irritation and the underlying cause of lung carcinoma in a significant number of cases. In fact, the right lower lobe, considered the most frequent location of bronchiectasis and pulmonary abscesses, was the primary site of lung carcinoma in only 8.6 per cent of cases and one of the least frequently involved lobes. In the majority of instances where bronchiectasis or chronic pneumonia was found, they occurred distal to the tumor mass and the natural assumption was that they were secondary manifestations of the tumor resulting from blockage of lymphatics and bronchi.

Active tuberculosis was present in only 1.6 per cent and healed parenchymal tuberculosis in 5.9 per cent. Thus, the total of 7.4 per cent is slightly less than that reported by Kikuth (quoted from Weller [5]) of 8.7 per cent, and is roughly in accord with the known incidence of tuberculosis in unselected cases. "Kikuth felt that tuberculosis plays a small rôle, if any, in determining a malignant pulmonary condition, occupying in this respect exactly the same position as a considerable number of other chronic inflammatory diseases."

Schmorl felt that the inhalation of dust and the presence of pneumoconiosis was of significance, especially in the production of lung carcinoma in the Schneeberg miners. Certainly, the frequency with which these conditions are associated at Schneeberg is more than coincidental and eventually a specific etiological factor may explain these cases. However, the relative infrequency with which these two conditions are associated elsewhere and in other mines lends doubt to the theory that the mechanical irritation is an etiological factor and it would seem more likely that the answer rests in some specific quality of the Schneeberg ore. In the present series of cases pneumoconiosis was found in only 2.9 per cent of instances, or in 2 cases, and in both of these the fibrosis was only of moderate degree. It would appear that pneumoconiosis is of insignificant importance in the production of lung carcinoma in general.

Associated extrapulmonary pathological findings were distributed as follows: pyelonephritis 13.4 per cent, cholecystitis and endocarditis 4.4 per cent each, pericarditis, acute pancreatitis and alcoholic cirrhosis 2.9 per cent each, mitral stenosis, chronic glomerular nephritis, peptic ulcer, diverticulitis, peritonitis and esophageal obstruction in 1.5 per cent each. These findings are not inconsistent with postmortem findings in unselected cases of an older age group predominantly male.

Pleural Cavities

Pleural effusion may result either from the inflammatory processes commonly associated with primary lung carcinoma or as a result of tumor implants on the pleural surfaces. The pleural cavities were involved by tumor in 39.3 per cent of cases, either by extension or metastasis. In 11 per cent there was fluid in both pleural cavities and in 32 per cent fluid was present only on the same side as the primary lung carcinoma. In 6 per cent fluid was present on the opposite side and in 50 per cent no fluid was present. Most frequently the fluid was described as serosanguineous; however, in many instances it was clear, colorless or yellow fluid. In 2.9 per cent of cases it was seropurulent and a definite fibrinous pleuritis was present, and in 1.5 per cent frank empyema existed as a result of a bronchial fistula. These latter conditions were found on the same side as the primary tumor.

Fibrous adhesions, evidence of healed pleuritis, occurred on both sides in 38 per cent; on the same side as the primary tumor only, in 54 per cent; and on the opposite side only, in 1.5 per cent. The pleural cavities were negative in 10 per cent of cases.

Adenocarcinomas showed a slightly greater tendency to involve the pleura with the accumulation of fluid and the production of adhesions than either of the other two types described.

Summary and Conclusions

1. Sixty-nine cases of primary carcinoma of the lung, verified at autopsy, have been presented and divided into three groups, namely: (*a*) squamous cell carcinoma, (*b*) adenocarcinoma, (*c*) undifferentiated carcinoma.

2. Squamous cell carcinomas constituted the largest single group and 42 per cent of the entire series. The left lung and upper lobes were the most common site of the primary tumor, and 61 per cent involved a bronchus. Cavitation in the primary tumor occurred in 17 per cent. Metastases and extensions were not so widespread as in the undifferentiated group, but were more extensive than in the adenocarcinoma.

3. Adenocarcinomas constituted 24 per cent of the series and were composed of 53 per cent mucinous carcinoma and 47 per cent non-mucinous carcinoma. These tumors probably all originated from the epithelium lining the bronchi or from the peribronchial mucous glands. The mucinous type frequently metastasized and occasionally extended, but appeared less malignant than the non-mucinous group. They involved bone more frequently than any other type.

Non-mucinous carcinomas were the least malignant and were occasionally confined to a lobe or a lung. They frequently involved the pleura.

4. Undifferentiated carcinomas constituted 33 per cent of this series. Primary tumors occurred slightly more frequently in the left lung, always involved a bronchus and occasionally infiltrated an entire lung. This group showed the most vigorous tendency to metastasize widely and to extend locally.

5. All lung carcinomas in this series occurred most frequently in the left lung, in the upper lobes and at the hilum. Primary tumors were a single mass in 95.7 per cent of the cases and usually involved or occluded a bronchus. These carcinomas metastasized widely and primary tumors were very prone to extend regionally. Skeletal and intracranial metastases were common.

6. An absolute increase in the general incidence of lung carcinoma occurred at the Boston City Hospital in the period 1930 to August 1, 1934, and is possibly explainable as a selective phenomenon.

7. Males were affected predominantly and in the ratio of 1 female to 4.5 males. The incidence in males has increased in the past 15 years.

8. The majority of cases occurred in the 6th and 7th decades. Adenocarcinomas tended to occur more frequently at the extremes of life.

9. Associated pulmonary inflammatory conditions occurred in 58.8 per cent of the cases.

10. The incidence of pulmonary tuberculosis and pneumoconiosis in this series was consistent with the incidence in unselected cases.

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HISTOLOGICAL EFFECTS OF POTASSIUM IODIDE AND THYROID SUBSTANCE ON THE THYROID GLAND OF THE GUINEA PIG IN EXPERIMENTAL SCURVY *

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INTRODUCTION

1. The Effect of Potassium Iodide on the Thyroid Gland

The histological results of potassium iodide feeding on the normal thyroid gland of the guinea pig have been recorded by Gray,[1] Gray, Haven and Loeb,[2] Gray and Loeb,[3] Gray and Rabinovitch,[4] Loeb,[5-9] McCordock,[10] Rabinovitch,[11, 12] Rabinovitch and Gray,[13] and Silberberg.[14] They found that short periods of either oral or intraperitoneal administrations of potassium iodide (usual dose from 0.01 to 0.1 gm. of potassium iodide) cause a stimulation of the normal thyroid gland. Rabinovitch [11] showed a definite relation between the amount of potassium iodide fed and the increase in proliferative activity of the epithelium, as estimated by the number of mitoses. Gray and Loeb,[3] and Rabinovitch [12] noted that the action of the potassium iodide on the thyroid gland does not reach its maximum until after 16–18 days, this being the period of marked proliferation in normal guinea pigs.

Gray, Haven and Loeb,[2] Gray and Loeb,[3] Loeb,[5,7] and Rabinovitch [15] observed an entire cessation in mitotic activity after feeding potassium iodide for a period of 30 days because of the pressure exerted on the cells of the acini as a result of the increase in quantity of the colloid. Loeb [16] states that the colloid produced under potassium iodide stimulation does not leave the acini in a sufficient quantity but remains largely stored up in the gland, and by its injurious pressure on the walls of the acini may lead to a gradual inhibition of the glandular activity. In other words, it is possible that potassium iodide causes a retention of the thyroid hormone within the gland.

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2. The Effect of Thyroid Feeding on the Thyroid

Structural signs of inhibition in the activity of the thyroid gland, similar to those noted above, have been reported by Gray, Haven and Loeb,[2] Gray and Loeb,[3] and Gray and Rabinovitch [17] after oral administration of thyroid substance to normal guinea pigs. They also noted the number of mitoses to be lower than in the normal controls. According to Gray, Haven and Loeb,[2] in thyroid feeding an excess of thyroxin in the circulation prevents the mobilization of colloid in the gland, which thus remains solid. In addition, the thyroxin may perhaps gradually cause an atrophy of the epithelium as an expression of its inactivity.

3. The Thyroid Gland in Experimental Scurvy

Rondoni and Montagnani [18] observed hemorrhagic lesions of the thyroid gland as being characteristic in scorbutic guinea pigs. McCarrison [19–21] described a marked enlargement of the thyroid resulting in an increased weight of the gland, sometimes amounting to two or three times the weight of that in the healthy animal. When he examined these glands histologically he found the enlargement to be due mainly to hemorrhagic infiltration of the organ. He concludes that a scorbutic diet of crushed oats and autoclaved milk may cause a considerable enlargement of the thyroid gland in guinea pigs. Bessesen [22] also found an irregular enlargement of the thyroid in various stages of experimental scurvy in guinea pigs.

Löwy [23] found no histological changes in the thyroid gland during scurvy, as compared with the gland of normal control guinea pigs. Meyer [24] described thyroid glands of scorbutic guinea pigs as having a tendency to show a reduction in the amount of colloid and an increase in the amount of "intrafollicular (desquamated) cells," as he called them. He also noted these elements varied considerably in amount in the same gland, as well as in different thyroid glands. He states that his work is not inclusive enough (insufficient number of cases) to draw reliable conclusions and consequently he believes, along with Löwy, that no "noteworthy changes" take place in the thyroid glands of guinea pigs fed the scurvy-producing diet for 30 days.

Harris and Smith [25] studied the changes in the thyroid during chronic scurvy lasting 97 days. They reported a decrease in the

amount and an increase in the vacuolation of the colloid. This was accompanied by an increase in the height of the follicular epithelium and an increase in the number of interfollicular cells. They suggested that vitamin C might function in the regulation of iodine metabolism.

It is known that the thyroid is associated with iodine metabolism. Therefore, it was the purpose of this investigation to determine the histological effects of potassium iodide and thyroid substance on the thyroid gland in experimental scurvy, and to determine whether or not the administration of these iodine compounds would tend to prolong the life of scorbutic animals.

Material and Technique

Since young guinea pigs are more susceptible to scurvy than adults, only active individuals in good nutritive condition and weighing between 250 and 350 gm. were used. The control and experimental groups were divided equally with regard to sex. All of the experimental animals were kept at an approximately constant temperature. They were kept in individual sanitary cages with open wire-mesh bottoms to allow the excreta to fall through, thus tending to prevent coprophagy and eliminate any source of vitamin C that might occur in this manner. The cages were cleaned thoroughly at regular intervals.

The animals were housed in their respective cages and fed the basal ration plus green food, both *ad libitum*, and also 3 cc. of orange juice daily for a week before the beginning of the experimental period. During this period of observation attention was paid to general activity and willingness to eat the "synthetic" ration. The experiment proper was then begun by discontinuing the green food and continuing the administration of orange juice to the control, starvation, and chronic scurvy animals, as indicated below, but not to the animals on the acute scurvy diet. The animals were divided into groups and fed diets and iodine compounds respectively, as indicated in Table I. The diets used were as follows.

Scurvy-Producing Diet (Basal Diet): This consisted of alfalfa meal and wheat flour, mixed in equal amounts by weight and moistened with water. Whole oats and tap water were supplied *ad libitum*. The ration was prepared freshly every morning and a sufficient amount for one day was placed in low dishes in the cages.

Chronic Scurvy Diet: The basal diet plus 0.5 cc. of orange juice every second day.

Starvation Diet: Water and 1 cc. of orange juice were given daily.

TABLE I

Experimental Procedure

Animal groups	No. animals used	Days on experimental diet	Days on iodine compounds
Controls			
(1) Normal	6	0–110	0
(2) Normal +KI	4	31–111	11–55
(3) Normal +thyroid	2	31–118	31–53
Starvation	4	5–10	0
Acute scurvy			
(1) Iodine-free	2	21–29	0
(2) Iodine compounds from first day			
(*a*) KI	1	17	17
(*b*) Thyroid	1	14	14
(3) Iodine compounds after 21 days			
(*a*) KI	6	22–33	1–12
(*b*) Thyroid	6	23–31	2–10
Chronic scurvy			
(1) Iodine-free	2	56–126	0
(2) KI after 56 days	5	63–138	7–82
(3) Thyroid after 65 days	4	72–120	7–55
Total scorbutic animals			
(1) Iodine-free	4	21–126	0
(2) Iodine compounds			
(*a*) KI	12	17–138	1–82
(*b*) Thyroid	10	14–120	2–55

Normal Diet: The same kind and amount of food substances were given as were used in the scurvy-producing diet with the addition of 3 cc. of fresh orange juice daily, administered orally by pipette, to each guinea pig.

The dose of potassium iodide consisted of 0.01 gm. (Merck's C. P. granular potassium iodide) in 1 cc. of distilled water. A dose of thyroid substance amounted to 0.1 gm. (Lilly's U. S. P. thyroid, 1 gm. representing 5 gm. of fresh thyroid gland) in 1 cc. of distilled

water. These solutions were administered daily by mouth through pipettes.

The animals were weighed at 3 day intervals, except in the starvation experiments, in which they were weighed daily.

In all animals on the scurvy diet typical and usually severe symptoms of scurvy developed. When they had reached the stage of advanced scurvy, and almost at the point of death in the acute scurvy cases, chloroform was administered and both lobes of the thyroid gland were immediately removed and placed in Zenker's fixative. They were embedded in paraffin, sectioned at 7μ thickness in complete serial sections, and stained with Delafield's hematoxylin and eosin. These stains were found to be satisfactory in bringing out both the cytoplasmic and nuclear structures.

The following points were considered in studying the slides: (1) condition of follicles, (2) colloid, (3) epithelium, (4) interfollicular cells, and (5) phagocytes. Sections from approximately the same areas of the thyroid gland were used in these studies.

Results

1. *Effects of Various Diets on the Condition of the Animals*

The weight curves obtained were typical and characteristic of the diets on which the animals had been placed. They were similar to those given by Hess.[26]

The animals receiving 3 cc. of orange juice daily appeared to be in good health and active throughout the entire experimental period. Those on the starvation diet did not exhibit any symptoms of scurvy. The animals fed only the basal diet lived from 14 to 33 days, with an average of 28.2 days, on account of the development of acute scurvy. However, the animals that received 0.5 cc. of orange juice every second day, in addition to the regular basal diet, exhibited chronic paralysis, soreness to touch, fragility of bones, decreased consumption of food with loss of weight, and lived from 56 to 138 days, with an average of 97.7 days. In some cases there was no paralysis of the limbs, even though other symptoms developed. In many instances the teeth were broken off, but this was never seen in normal controls. The histological results are presented in tabular form in Table II.

2. The Normal Thyroid Gland

In the normal thyroid gland, as a general rule, the follicles are rounded, regular and medium in number and size. The epithelium appears in most cases to be cuboidal, with an average or medium height and with round nuclei, as shown in Figure 1. Phagocytes which are located in the colloid are few in number. There is considerable variation in the quantity of colloid of the normal thyroid, as revealed by a comparative study of the various glands. It is uniformly stained but varies considerably in vacuolations from practically solid (Fig. 1) to extreme vacuolations throughout. However, this extreme vacuolation is probably exceptional, being observed in only 1 case. At times the colloid fills the follicles completely, whereas in other cases it is greatly retracted from the follicular wall. This condition may be due to shrinkage effects produced during preparation of the material. The latter two conditions may occur in the same gland, but usually one condition alone is found throughout.

Starvation from 5 to 10 days had practically no effect on the thyroid gland, as compared with the normal, since they are very similar in most respects. The most noticeable difference is that the colloid is not as uniformly stained as in the normal.

3. The Effect of Potassium Iodide on the Thyroid Gland

Potassium iodide causes the follicles to become irregular in shape, and larger in size, as seen in Figure 2. There is a decrease in number of follicles since they unite with one another (Fig. 5). The colloid is not uniformly stained and is usually retracted slightly from the follicular wall. In short periods of administration (14 days) the colloid is soft, always peripherally vacuolated, and frequently honeycombed throughout, but not increased in amount. The epithelium is slightly higher and phagocytes are numerous. However, there is a characteristic change during longer periods of administration (55 days), as noted in Figure 2. The colloid becomes harder, more solid, less vacuolated and more abundant. The epithelium, because of the pressure exerted on it by the colloid, becomes low, flat, thin and rectangular, with flattened nuclei. Many cases are seen where the thinness results in a break in the follicular wall and a consequent

TABLE II

Experimental Results

Animal groups	Microscopic findings			
	Follicles	Colloid	Epithelium	Interfollicular cells
Controls				
(1) Normal	Rounded, regular, medium size and number	Uniformly stained, peripherally vacuolated	Cuboidal, average height, with round nuclei	Average number
(2) Normal +KI	Irregular, slightly increased in size	Slightly increased, non-uniformly stained, peripherally vacuolated, frequently honeycombed	Low, flat, thin, rectangular with flattened nuclei	Decreased number
(3) Normal +thyroid	Numerous, small, irregular	Non-uniformly stained, non-vacuolated	Cuboidal, medium height, with round nuclei	Slightly increased
Starvation	Same as control	Non-uniformly stained, otherwise like control	Same as control	Same as control
Acute scurvy				
(1) Iodine-free	Irregular, reduced in number	Non-uniformly stained, reduced, peripherally vacuolated, sometimes honeycombed	Very high, elongated, nuclei round	Increased
(2) (*a*) KI after 21 days	Small, rounded, average number	Non-uniformly stained, slightly vacuolated peripherally, sometimes honeycombed. Average amount	Tends to be low, flat, thin, with flattened nuclei	Average number
(2) (*b*) Thyroid after 21 days	Small, irregular, average number	Non-uniformly stained, solid, average amount	High, elongated, with round nuclei	Average number
Chronic scurvy				
(1) Iodine-free	Small, irregular, slightly below average number	Decreased, non-uniformly stained, peripherally vacuolated, sometimes honeycombed	High, elongated with round nuclei	Increased
(2) KI after 56 days	Average number and size, irregular	Non-uniformly stained, average amount, solid, increased in long periods of feeding	Low, flat, rectangular with flattened nuclei, breaking through in many places	Reduced
(3) Thyroid after 65 days	Average size and number, irregular	Non-uniformly stained, sometimes vacuolated, slightly increased in long periods of feeding	High, elongated, with round nuclei	Slight increase

coalescence of the colloid contained within (Fig. 5). There is a reduction in number of the interfollicular cells, and phagocytes are not so prevalent, being represented as degenerated structures appearing as dark spots in the colloid (Fig. 2).

4. The Effect of Thyroid Feeding on the Thyroid Gland

Thyroid substance also causes the follicles to become irregular and small, but more numerous as shown in Figure 3. The colloid is non-uniformly stained, retracted greatly from the follicular wall, average in amount and non-vacuolated. The epithelium in most cases is cuboidal, of medium height with round nuclei. There is a slight increase in the number of interfollicular cells and phagocytes are rare.

5. The Thyroid Gland in Experimental Scurvy

(*A*) *The Thyroid in Chronic and Acute Scurvy:* Chronic scurvy of 126 days duration, without the addition of any iodine compounds, causes more marked changes in the thyroid (Fig. 4) than acute scurvy. The follicles have a higher epithelium and are more irregular and reduced in number. The non-uniformly stained colloid is more vacuolated peripherally and sometimes throughout, and further reduced in amount, tending to disappear entirely from many of the follicles. There is a tendency for the epithelium, which is high with round nuclei, to become columnar. The interfollicular cells are increased in number but the phagocytes are very scarce. These changes are not so marked in chronic scurvy lasting for 56 days. Likewise, these conditions are more marked in animals fed the basal diet alone for 29 days than in those on the same diet for 21 days.

(*B*) *The Effect of Potassium Iodide in Experimental Scurvy:* Potassium iodide administered to scurvy guinea pigs produced similar changes in the thyroid (Fig. 5) as described above for the normal gland (Fig. 2). The histological changes were not as noticeable in short periods of administration, in either acute or chronic scurvy, as they were in longer periods.

(*C*) *The Effect of Thyroid Feeding on the Thyroid Gland in Experimental Scurvy:* The administration of thyroid substance to scurvy guinea pigs produces the same changes in the thyroid glands as has previously been described for the controls (Fig. 3). Thyroid glands

in the chronic scurvy condition, to which thyroid substance has been administered for a short time (7–11 days), resemble those of 126 day chronic scurvy (Fig. 4), whereas those in which the administration lasted much longer have a different appearance, as noted in Figure 6. Long periods of thyroid administration cause the gland to return to a condition similar to that of the normal. In other words, it appears that potassium iodide and thyroid substance offset the action of scurvy on the thyroid gland, causing a decided change in its histological appearance.

Observations were made to determine whether or not potassium iodide and thyroid substance would prolong the life of the animal in experimental scurvy. Animals on the basal diet plus potassium iodide had an average life of 28 days, whereas those on the same diet, with the addition of thyroid substance, lived on the average 28.5 days. Thus, in the cases studied it was noted that these iodine compounds did not tend to prolong the life of the individuals, since Sherman and Smith [27] found the survival period of scorbutic animals to vary from 26 to 34 days.

Discussion

The normal thyroid glands described above compare very favorably with those described by Loeb,[5-9] Gray,[1] Rabinovitch,[11,12] McCordock,[10] and others. One exception to the general conditions was observed in which there was an excessive amount of vacuolation.

The glands from animals on a starvation diet (5–10 days) appeared like those of the controls in every way except that a difference in the staining power of the colloid was noted. Rondoni and Montagnani,[18] Löwy,[23] and Harris and Smith,[25] likewise found no significant histological changes in the structure of the thyroid gland in guinea pigs as a result of starvation.

The histological changes occurring in the thyroids of guinea pigs with experimental chronic scurvy are similar to those previously described by Harris and Smith [25] in chronic scurvy of 97 days duration. They likewise found similar changes, but less marked, in acute scurvy. Hemorrhagic infiltrations, as observed by McCarrison,[20] and Rondoni and Montagnani,[18] were seen to a slight extent in the normal animals, but were more noticeable in acute scurvy of 29 days and considerably greater in chronic scurvy of 126 days duration.

Whether they are extensive and great enough to cause the increased weight observed by McCarrison is not known.

The histological results of potassium iodide feeding reported in the present work (Fig. 2) agree with those of other workers. Furthermore, it seems that potassium iodide has the same action on the thyroid gland in acute and chronic scurvy (Fig. 5) as it does on a normal gland (Fig. 2), when administered for a corresponding period of time. That is, potassium iodide seems to offset the action of scurvy on the thyroid, and instead induces its own characteristic effects. The idea of Loeb [16] that potassium iodide causes a retention of the thyroid hormone within the gland, might serve as an explanation for the increase of colloid observed, and the failure to observe the histological changes characteristic of scurvy, as described by Harris and Smith,[25] and the writer.

It was found that administration of thyroid substance to normal guinea pigs causes morphological indications of inhibition in the activity of the thyroid gland, as reported by earlier investigators. The hypothesis of Gray, Haven and Loeb [2] that the increased amount of thyroxin in the circulation due to thyroid feeding does not allow the mobilization of colloid in the gland, might explain why the colloid, in the case of feeding thyroid substance to chronic scurvy guinea pigs, does not become vacuolated and reduced, as it does in iodine-free chronic scurvy. The administration of thyroid substance in acute and chronic scurvy (Fig. 6), causes a definite and decided change toward the condition in the normal gland during thyroid feeding. This change is more pronounced in the longer periods of administration.

The fact that the administration of iodine compounds seemed to cause the thyroid to approach its normal condition in the absence of vitamin C, without prolonging the life of guinea pigs in experimental scurvy, seems to indicate that vitamin C is not concerned with iodine metabolism, as suggested by Harris and Smith.[25]

Summary and Conclusions

1. The thyroid gland in scurvy presents irregular follicles with higher epithelium, a reduced amount of non-uniformly stained but extensively vacuolated colloid, and an increase in the interfollicular cells. These changes are more marked in chronic scurvy of long duration than in acute scurvy.

2. Potassium iodide, when administered to animals with scurvy, causes a decrease in the number of vacuoles and an increase in amount of the colloid, accompanied by a flattening of the epithelium and a decrease of the interfollicular cells. Thyroid substance produces similar results except that the epithelium is not flattened but is returned to the normal medium height.

3. Potassium iodide and thyroid substance, in the doses administered, do not tend to prolong the life of the animal in experimental scurvy. Thus, it appears that vitamin C is not concerned with iodine metabolism.

NOTE: The writer wishes to express his deepest appreciation to Dr. D. Ludwig for his advice and careful criticism throughout the course of this investigation.

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DESCRIPTION OF PLATES

PLATE 63

FIG. 1. Photomicrograph of a section of a normal gland. Female, on diet 21 days. The follicles are rounded, regular, and medium in size and number. The epithelium is cuboidal, of average or medium height with round nuclei. The interfollicular cells are average in number. There are a few phagocytes. The colloid is practically solid but slightly retracted. × 800.

FIG. 2. Photomicrograph of a section of thyroid gland of a female guinea pig fed a normal diet for 56 days before the administration of potassium iodide. Potassium iodide then given for 55 days. Decreased number of irregular follicles. Colloid less vacuolated and more abundant. Low, flat, thin epithelium with flattened nuclei. Reduction of interfollicular cells. Dark spots in the colloid represent degenerated phagocytes. × 800.

FIG. 3. Photomicrograph of a section of thyroid gland of a male guinea pig fed a normal diet for 53 days before the administration of thyroid substance. Thyroid substance then given for 65 days. Irregular follicles. Colloid greatly retracted but average in amount and non-vacuolated. Cuboidal epithelium. Degenerated phagocytes are rare. × 800.

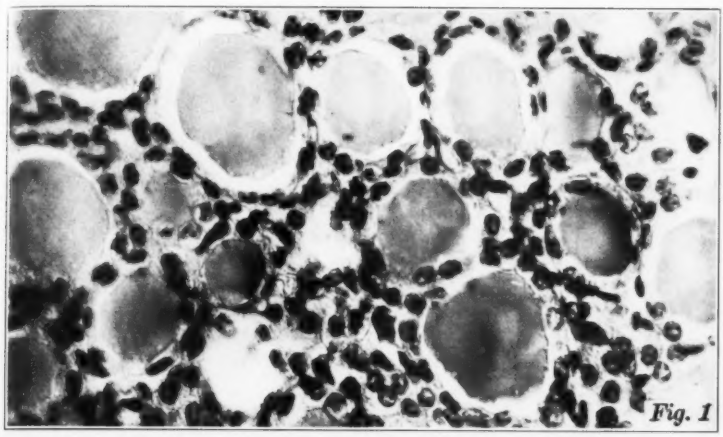

Fig. 1

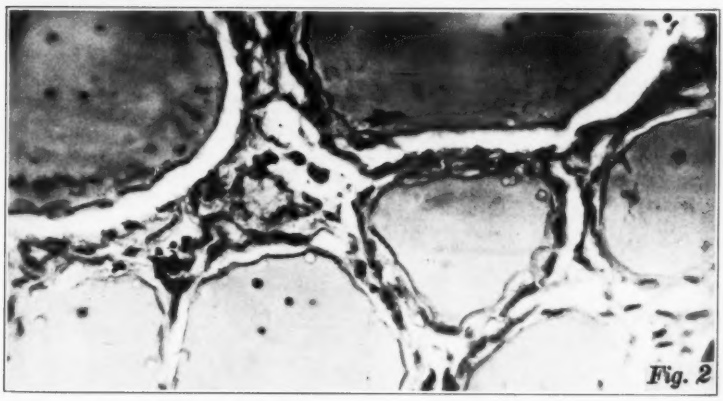

Fig. 2

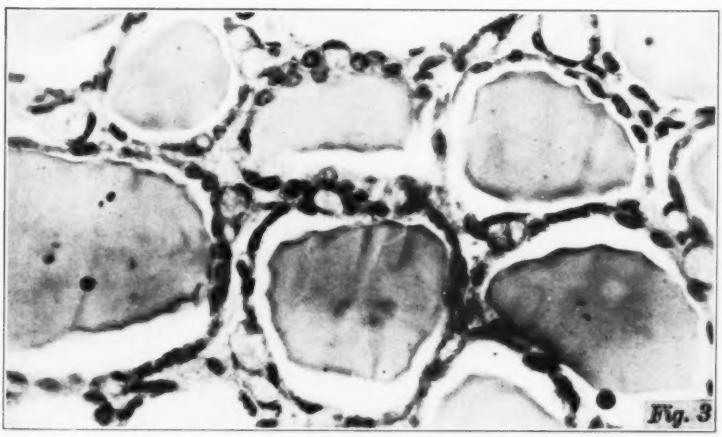

Fig. 3

PLATE 64

FIG. 4. Photomicrograph of a section of thyroid gland of a male guinea pig fed a chronic scurvy diet alone for 126 days. Irregular follicles with very high epithelium. Colloid extremely vacuolated and tending to disappear from the follicles and thus reduced in amount. Increased number of interfollicular cells but phagocytes are scarce. × 800.

FIG. 5. Photomicrograph of a section of thyroid gland from a female guinea pig fed a chronic scurvy diet 56 days before the administration of potassium iodide. Potassium iodide then given for 82 days. Union of colloid after the follicular wall is broken. Increase in rarely vacuolated colloid in the irregular follicles. Low, flat, thin epithelium about to break through in many places. Phagocytes are rare. × 800.

FIG. 6. Photomicrograph of a section of thyroid gland of a female guinea pig fed a chronic scurvy diet for 65 days before the administration of thyroid substance. Thyroid substance then given for 55 days. Increase in colloid and decrease in interfollicular cells, as compared to Figure 4. Colloid retracted but non-vacuolated. × 800.

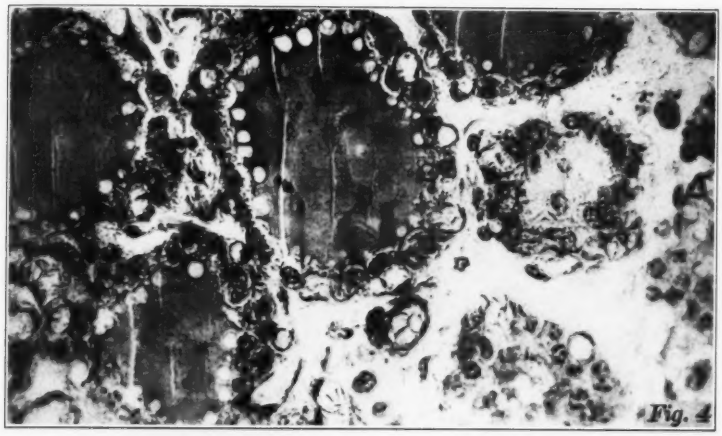

Fig. 4

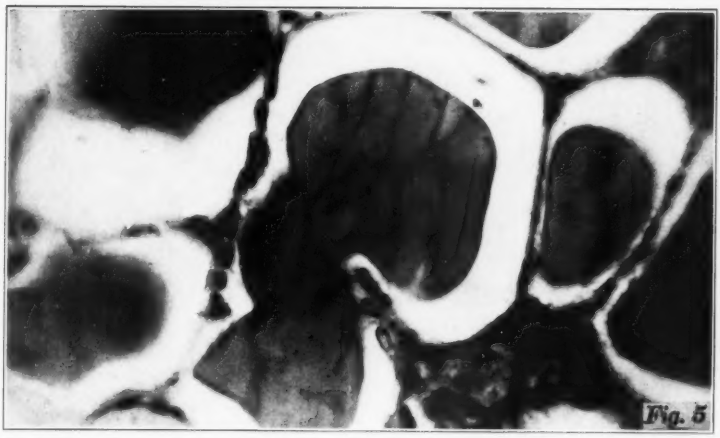

Fig. 5

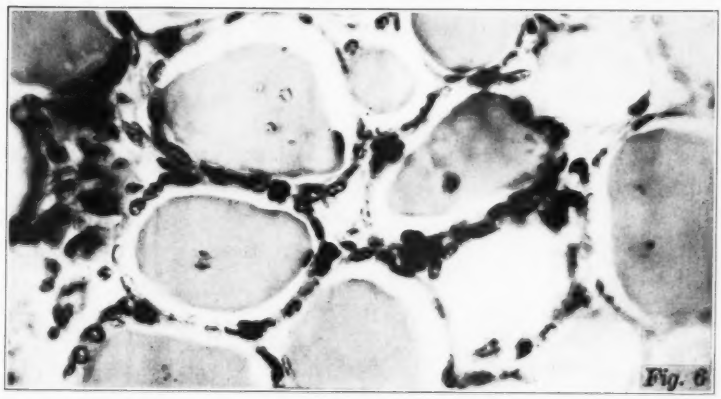

Fig. 6

GLOMERULAR CHANGES IN ARTERIOSCLEROTIC CONTRACTION OF THE KIDNEY *

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In the course of systematic investigations on arteriosclerotic contraction of the kidney, I have paid special attention to the changes in the basement membrane of the glomerulus and its capsule.

The following communication is confined to degenerative changes and is not concerned with inflammatory processes. Furthermore, those degenerative changes that are due directly to lesions of the vas afferens are not considered. The method of glomerular destruction associated with hyaline or fatty degeneration of the vas afferens — whether due to obstruction of the blood stream or to immediate encroachment upon the glomerular capillaries — is so well known that my investigations could not possibly add anything new. It appears that less attention has been paid to degenerative changes not associated with visible disease of the vas afferens, in spite of their far greater frequency. The reason, apparently, is that the earlier stages of glomerular atrophy become conspicuous only with special stains. The Lee-Brown stain has proved quite adequate for this purpose and is simple in practice.

Two different forms of glomerular degeneration can be distinguished, a primary and a secondary. Both forms can lead to the same terminal destruction.

PRIMARY (SENILE) DEGENERATION

Axial Increase of Connective Tissue

The primary form consists of a thickening of the connective tissue framework of the glomerular tuft. When the basement membrane and the connective tissue are demonstrated by the Lee-Brown stain, the delicate subepithelial membrane stands out sharply delineated and is not thickened. The central axis of the glomerular lobule, on

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the other hand, is more marked, stains a deep blue and shows a blurred outline. Even under low power the lobulation of the glomerulus is accentuated by this broadening of the axial supporting tissue (Fig. 1). The fact that on cross-section the delicate basement membrane can be distinguished clearly from the thickened axis, on which it lies tangentially, proves definitely the separate existence of the latter as a mass of intercapillary connective tissue.

The presence of such a structure has long been denied, but the result of research in normal anatomy leaves no doubt that the glomerular tuft contains fibrillary nucleated connective tissue between the capillaries, in addition to the epithelial cells, the endothelial cells, and the basement membrane (Zimmermann, von Möllendorff and Borst).

In minor degrees of thickening this intercapillary connective tissue shows a fine fibrillary structure, but later becomes homogeneous and hyaline. The broadest masses of hyaline connective tissue are always found in the intraglomerular portion of the hilum. The other glomerular components (epithelium, endothelium and basement membrane) are quite normal. In the overwhelming majority of cases the vasa afferentia and precapillaries likewise are unaffected.

Since such a great number of glomeruli show the changes described above in otherwise normal kidneys, one might be inclined to regard this picture as a variation of the normal. There are, however, great variations of intensity and extent of this process in different kidneys. The degree of thickening and number of altered glomeruli both obviously increase with age. Although some arteriosclerotic and normal kidneys in old subjects show no thickening of the axial connective tissue, this feature was entirely absent in a control series of twenty individuals under 20 years of age. It proved impossible by counting those glomeruli to show any parallelism with any type of vascular change or with high blood pressure, which might possibly exist. Likewise, no relation can apparently be established to passive congestion of the kidney.

Although severe and extensive axial thickening was observed in 2 cases where the individuals were 32 and 45 years of age, nevertheless its greater frequency in older subjects is undoubted. This points to the conclusion that the change described cannot be regarded as a variation of the normal but is an expression of the aging process in the glomerulus.

Since MacCallum in a recent paper pays attention especially to the change of intercapillary connective tissue and states that the main group of such cases occurs in association with cardiac hypertrophy and arterial hypertension, I shall go more into detail in regard to this point.

It is true that the process of thickening of the wall of the vasa afferentia very often tends to enter into the glomerular tufts and that in these cases the secondary degeneration of the glomeruli is due to an increase in intercapillary connective tissue, which in later stages compresses the capillaries. However, it must be emphasized that the causal connection is confined purely to the arteriolosclerosis. The relation between arterial hypertension and arteriolar sclerosis still is a question. The object of this paper is to stress the fact that the "axial thickening" is a far more common finding and may very well occur independently of changes in the arterioles. When comparing this change with the heart weight, I found among 46 cases in which I enumerated the glomeruli with thickened connective tissue: (*a*) 6 cases of severe thickening with a heart weight under 400 gm.; 3 cases of severe thickening with a heart weight over 430 gm.; (*b*) on the other hand, 7 cases with a heart weight of more than 500 gm. had a degree of axial thickening ranging from zero to about half as much as in the cases of the first group.

It can be definitely stated, then, that this condition is independent of arterial hypertension and cardiac hypertrophy.

MacCallum speaks in these cases of a growth of the mesangium, but my histological examination never revealed any increase of nuclei unless there was an inflammatory process associated with the axial thickening. Because of this I cannot convince myself of an actual axial growth.

Considering the details of the process, one can state that the degeneration in question begins at the hilum where the capillaries branch, and progresses towards the periphery (Fig. 2). While the thickening is frequently confined to the region of the hilum, I have never seen peripheral broadening of the connective tissue in a glomerulus with a normal hilum.

In consequence of this process, collapse of the capillaries occasionally develops. In some rare instances this collapse is confined to one glomerular lobe, of which the axis is definitely thickened, while its subepithelial membrane is still unaffected. One might, then, justifi-

ably assume that the collapse and the axial thickening are closely related. In the later stage of hyalinization, which of course involves the basement membrane, it is impossible to make any such distinction.

It should be mentioned that the thickening of the intercapillary connective tissue can occur also in connection with other processes.

We not infrequently encounter cases in which the intercapillary change is so marked and so extensive that one might be inclined to look upon this disease of the kidney as a characteristic lesion. A later paper will be devoted to a closer study of these kidneys. The axial thickening may develop in amyloid degeneration or subsequent to inflammatory lesions and can be demonstrated in the glomerular destruction which follows primary thickening of the basement membrane. Instances of the latter, however, as we shall see later, are decidedly uncommon. Axial thickening has been mentioned several times in recent papers (MacCallum, Schürmann and MacMahon), although associated with other conditions. It must be emphasized, however, that this lesion in its pure form is exceedingly frequent and independent of changes in tubules and blood vessels; hence it has been termed "primary degeneration."

Secondary Degeneration

Thickening of the Basement Membrane

This description applies to glomeruli whose basement membrane is thickened (for the most part uniformly) and has a wrinkled appearance. The glomeruli are simplified in structure as a result of atrophy and for this reason are easily recognizable by special stains under low power. These lesions of the glomerulus have been described repeatedly and in excellent detail by McGregor. I shall therefore take her conclusions as a basis for the following considerations.

McGregor introduced the term "hypertensive glomeruli," assuming that a close connection exists between this form of glomerular disease and arterial hypertension. Her investigations failed, however, to shed any light on the pathogenesis of the glomerular lesions. A definite relation to arteriolar sclerosis could not be established, as partial or complete hyalinization of the vessels could be found only at some distance from the glomeruli they supplied. The author

herself was apparently not satisfied with the morphological relationship as the basis of the glomerular lesion.

I have tried to confirm the results that McGregor obtained by counting the hypertensive glomeruli. It can certainly be shown that the number of these "membrane-thickened" glomeruli is considerably increased in kidneys with severe arteriosclerosis. One should, however, regard quantitative observations on histological preparations with more skepticism. In enumerating the glomeruli it is impossible to avoid subjective errors which are present in the "birds-eye view" method of estimation. We are easily led thereby to form an impression with a false sense of certainty. Even if sections are taken from several parts of the kidney the method is still inaccurate owing to topographical variations.

Thus, counting every glomerulus throughout the section, I found a high percentage of so-called hypertensive glomeruli in simple, scarred, atrophic, senile kidneys without any relation to high blood pressure. The difference between McGregor's and my results might possibly be explained by the varying size of the scars in which the hypertensive glomeruli are crowded. I encountered cases in which the so-called hypertensive glomeruli could not be demonstrated anywhere else but in the vicinity of an old scar (Figs. 3 and 4). According to McGregor's own statement, she believes that this glomerular change depends on a circulatory damage. As we shall see later, I agree entirely with this point. I also believe that the thickening of the basement membrane is due to an ischemic process.

I encountered several cases of severe hypertension with moderate arteriosclerosis of the kidney in which only very few glomeruli with thickened basement membrane were present. As is well known, arterio- and arteriolosclerosis are frequently found in association with a previous history of hypertension. This, in my opinion, however, can be interpreted as a coincidental relationship rather than one of cause and effect. Inasmuch as I have found the distribution of the so-called hypertensive glomeruli to be a focal one related to vessel change, and therefore probably caused by ischemia, I prefer the term ischemic glomerulus for this type of change.

Two types of glomeruli with thickened basement membrane can be distinguished. The first is characterized by additional thickening of the capsular membrane with only slight widening of the capsular space, because of atrophy of the glomerular tuft itself. The second

shows definite dilatation of capsular space with no thickening of the capsular membrane. The combination of both these types is possible but the differentiation between them is necessary since the common occurrence of the pure form of either type strongly indicates their different histogenesis.

Ischemic Atrophy of the Glomerulus with Thickening of the Capsule

The majority of the vasa afferentia of this type of glomerulus are normal, although partial hyalinization of the vessel wall may be encountered occasionally, but not constantly, some distance proximately. In view of the inconstance of this finding, it is most improbable that a direct relation exists between this type of glomerular lesion and degeneration of the arteriole or prearteriole. Furthermore, one can practically never recognize with certainty any associated thickening of the axial connective tissue.

It is obvious that the process from the beginning consists of the thickening of epithelial basement membrane, but the change is confined for the most part to the glomerulus and only exceptionally extends to the basement membrane of the tubules. This type of glomerular degeneration has often been noted on account of the associated thickening of the capsule, which is easily demonstrable by the common staining method hematoxylin-eosin and Van Gieson, (Tschistowitsch, Roth, Herxheimer, Fahr and Aschoff). The onset of the process is usually observed at the site of reflecture of the basement membrane of the capsule to the capillary tuft, but may sometimes be particularly marked at the pole opposite to the hilum (Fig. 5). The contributions in the literature are purely descriptive. The mode of development of this special form of glomerular atrophy is still in question.

On the negative side we can first state, contrary to the assumption of most authors, that in all these numerous cases capillary collapse is not the result of mechanical narrowing of the vas afferens. The vessel is intact and very frequently shows passive congestion with dilatation of the lumen (Fig. 6). This of course does not apply to the exceptions mentioned in the introduction.

Two modes of development are to be considered: (1) ascending, due to obstruction of excretion; and (2) primary circulatory damage of low degree.

We can exclude the first mode in the above glomerular degeneration since no dilatation of the capsular space or the corresponding tubules is present, and without this criteria such a conclusion would not be justified.

On the other hand, there is adequate evidence to support the second mode of development. Membrane-thickened glomeruli are aggregated in so-called incomplete infarcts (Fahr), that is, wedge-shaped areas where the glomeruli are crowded between atrophic tubules. Although in hematoxylin-eosin preparations the glomeruli frequently appear normal, the special stains show thickening of the basement membrane. At the apex of such wedge-shaped areas one can as a rule recognize the arteriosclerotic narrowed vessels.

The glomeruli with thickening of the basement membrane and capsule are almost invariably aggregated together, but even if they occur isolated the corresponding tubular apparatus is atrophic (Fig. 7). In a doubtful case, serial sections will reveal the association of the glomerular and tubular atrophy. The tubular basement membrane, however, is rarely thickened, and there is little more than a slight broadening of the loose interstitial connective tissue.

It is, therefore, desirable to discuss the relation of the tubular atrophy to the glomerular change. In the majority of the atrophic scars the obliteration of the glomerulus is considered to be primary, atrophy of the tubules occurring as a secondary process (Fahr, Aschoff, Loehlein, Stoerk, Jores and Herxheimer). Opinions differ, however, as to the mechanism. On the basis of Stoerk's assumption of a vascular unit, that is, of a tubular blood supply via the glomerulus, the tubular atrophy is of circulatory origin. Other authors (Jores, Herxheimer, and others) favor the hypothesis of a disuse atrophy. Aschoff's explanation of the tubular atrophy resulting from excretion of toxins by the glomerulus appears to be only a theoretical possibility.

Certain qualifications are made by Herxheimer and Fahr in special cases, since they pointed out the possibility of a combined atrophy depending on narrowing of the larger vessels, in which case tubular might precede glomerular atrophy.

It has only lately been emphasized by Staemmler that the above possibility is most frequent in arteriosclerotic contracted kidneys. The proof lies essentially in the fact that according to this author the glomeruli are fairly well preserved even when tubular atrophy is very

advanced. The special stains, however, reveal in such areas many glomeruli with a thickened basement membrane. The same holds for smaller areas which contain only a few nephrons.

It is not to be denied that a primary lesion of a vas afferens often enough leads to destruction of the glomerulus and subsequently to atrophy of the tubules. In view of the early changes in the glomerular basement membrane, one gets the impression that the significance of such processes in contraction of the kidney has been overrated. Hyalinization or fatty degeneration of the vas afferens, which in fact leads to narrowing of the lumen with subsequent damage of the glomerulus, in absence of sclerosis of the larger vessels, affords a rare exception. In this respect I disregard the frequent hyalinization of arterioles without change of their lumen. Thus, it is quite immaterial whether the tubules receive their blood supply via the glomeruli or directly (Elze and Dehoff). The essential point is that tubular atrophy is purely circulatory, as is evident from the sequence of events; atrophy of tubular epithelium and thickening of the capsule membrane can often be recognized before any change can be demonstrated in the glomerulus. Furthermore, the microscopic picture leaves no doubt that the process may encroach on the glomerulus from the capsule, especially at the hilum, without involving the vessel at all. It is striking how long the capillary epithelium is preserved.

The fact that the tubular epithelium is much more susceptible to nutritional disturbance than the glomerular capillary apparatus also makes this sequence of events most probable. It has recently been shown in a paper by Maatz that a relatively short constriction of the large renal vessels produces in the first place, and chiefly, tubular atrophy. I believe also that the same explanation applies to the "tubular kidney atrophy" which Baehr produced by injection of iodine, particularly as the vessels showed marked changes.

Finally, we must mention another possible mode of development of atrophic scars described by Fahr and later by Helpap; namely, ascending contraction due to primary sclerosis of the medulla. The histological resemblance of these cases to ascending pyelonephrotic contraction suggested this conception to Fahr. Definite proof, however, is difficult to obtain. Whether we assume with Fahr a collapse of the lower parts of the tubules, or whether we postulate pressure from without, we should expect to find stagnation of secretion with

subsequent ascending dilatation. This, however, usually does not occur.

On the other hand, we know that distention of the pelvis produces ischemia of the kidney. Hinman and Morison have given conclusive experimental illustrations of this. It appears, therefore, that the same mechanism which we postulate in incomplete infarctions might come into play in ascending infection or pyelonephrosis. The histological appearances are in fact extraordinarily similar. Histological differentiation is indeed possible only in the presence of a characteristic distribution of the inflammatory infiltration. The type of contraction is itself identical. Fahr's conception of ascending contraction following primary sclerosis of the medulla is only tenable if sclerosis of the large vessels can be excluded on the one hand, and urinary obstruction, on the other hand, is demonstrable.

Ascending Atrophy

This form of glomerular atrophy with thickening of the basement membrane not infrequently occurs in arteriosclerotic kidneys. Small and large cysts are present in the renal cortex, representing dilated capsular spaces, in which often only a residue of the glomerular tuft can be recognized. Although Beer in 1904 described in detail these small glomerular cysts and stated numerically that 31 per cent of all degenerating glomeruli underwent this cystic change, only scanty information about them is found in the text-books.

In my experience the process, though very frequent, seems to be less common than is claimed by Beer. This author did not take account of the fact that hyalinized glomeruli may disappear completely. This alone invalidates any method of comparative enumeration.

Staemmler and Masugi pointed out, and Moritz and Hayman furnished the experimental proof, that hyalinized glomeruli can disappear without leaving any trace. The basement membrane of the glomerulus in ascending atrophy is usually quite uniformly thickened and wrinkled, but in contrast to the findings in ischemic atrophy (Fig. 8) the capsule largely remains unaffected (Fig. 9). The vas afferens is almost invariably patent and the glomerulus shrinks more and more, although capillaries are wide open and filled with blood. Here, too, surprisingly enough, the epithelial cells are often well preserved to the end and not even flattened in every case. The excessive

dilatation of the capsular space which is filled with coagulum points to a primary obstruction to secretion.

In spite of careful examination, Beer could not find any actual occlusion at the outlet of the capsular space and therefore assumed that constricting bands of connective tissue might lead to obstruction some distance from the glomerulus. Indeed, if we follow these cysts in serial sections we observe that the dilatation need not be confined to the glomerular capsule but sometimes involves one or several loops of the convoluted tubules. Here, in fact, one often finds a band-like increase of connective tissue just where the dilated tubule ends, sometimes rather distant from the glomerulus, showing that passive stagnation of secretion might be verified histologically. I agree with Beer's statement that the picture is often so complicated that a single nephron cannot be traced, especially when, as is frequently the case, the glomerular cysts are grouped together. However, it is in this type of case that reticular, scarring fibrosis is seen to be the cause of stagnation (Fig. 10).

Aschoff's assumption that these cysts are due to a developmental abnormality is most improbable. They indeed resemble the dilatation of the capsular space, which is so frequently found, especially in the outer zone of the cortex of the kidney of young infants, and which undoubtedly is due to malformation. Aschoff believes that such cysts increase in size with age and become particularly visible when the kidney contracts in old age, or as a result of inflammation. This explains why they are relatively rare in kidneys of young individuals without arteriosclerosis and why they seem to be more common in old subjects. In such arteriosclerotic kidneys, however, we see the cysts in all stages of development and it is inconceivable that the capsular dilatation should be preserved from infancy to old age, especially as we know that many glomeruli become obliterated and disappear on account of this process in early childhood (Herxheimer).

Cystic degeneration of the glomeruli, which is beyond doubt caused by stagnation of excretion, frequently is due to scarring processes in the vicinity of the glomeruli. Furthermore, it is conceivable that in primary tubular atrophy the epithelial cells may obstruct the lumen. Cases in which the cysts are accompanied by a thickening of the capsule afford evidence of such a process actually taking place. For we have seen above that thickening of the capsule and atrophy of the tubular epithelial cells are associated together in ischemic

atrophy. This combined picture is frequently encountered in incomplete infarcts and scars (Fig. 11).

Conclusions

In arteriosclerotic kidneys the following degenerative changes can be recognized in the glomeruli:

1. Primary broadening and hyalinization of the intercapillary axial connective tissue. This very frequent change is interpreted as an aging phenomenon of the glomerulus and may lead to secondary damage to the glomerular capillaries.

2. Thickening of the basement membrane, which is always secondary, may be due to two different causes:

(A) Ischemic atrophy of the glomerulus which may result from:

(*a*) Direct encroachment of hyalinization of the vas afferens upon the glomerulus leading to collapse and degeneration of all glomerular elements.

(*b*) Narrowing of the larger vessels, producing slow circulatory atrophy of the tubules and glomeruli. This change, the most common in all forms of arteriosclerotic kidneys, is characterized by thickening of the capsule and basement membrane, frequently extending from the former to the latter. This thickening of the capsule is closely associated with atrophy of the tubular epithelium.

(B) Ascending atrophy. This is caused by obstruction of the corresponding tubules and is characterized by the thickening of the capillary basement membrane without thickening of the capsule and is associated with dilatation of the capsular space. This form usually is not observed in pyelogenic ascending contraction. The latter is interpreted mainly as an ischemic process, thereby explaining the fact that in this condition we so frequently encounter a high degree of capsular thickening (*vide* (A) (*b*)).

Tubular atrophy in arteriosclerotic kidneys is chiefly a circulatory one and essentially depends on changes in medium sized and larger vessels.

Note: The author wishes to express his gratitude to the Committee in Aid of Displaced Foreign Physicians and the Rockefeller Foundation for a grant which made possible the above investigation,

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DESCRIPTION OF PLATES

PLATE 65

FIG. 1. Accentuated connective tissue framework of the glomerulus "axial thickening."

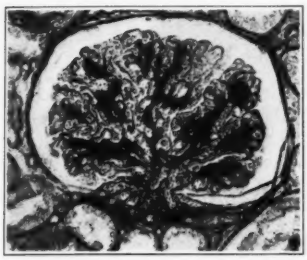
FIG. 2. "Axial thickening" progressing from hilum to periphery.

FIG. 3. Old scar with hyalinized glomeruli and five so-called "hypertensive glomeruli."

FIG. 4. Two "hypertensive glomeruli" of the same scar (Fig. 3) in high magnification.

FIG. 5. Capsular thickening. Process encroaching upon basement membrane. Most of the basement membrane still delicate.

FIG. 6. Same as Fig. 5. Vas afferens intact and congested.



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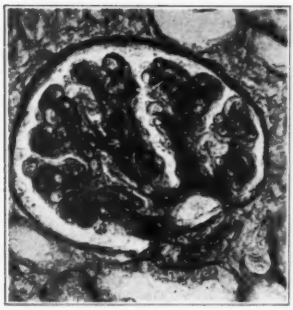

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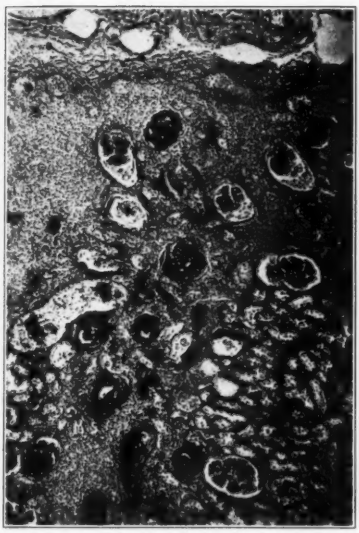

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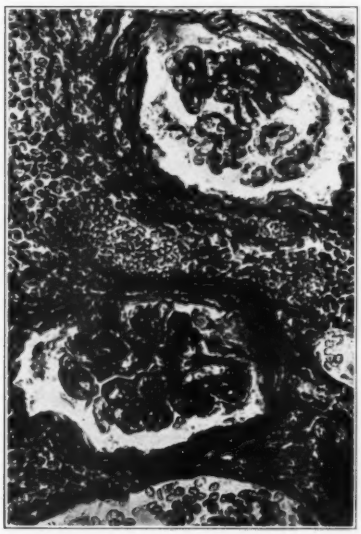

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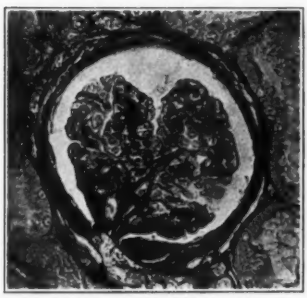

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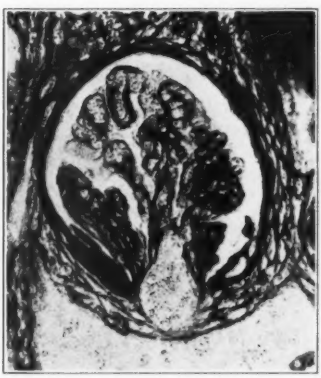


6

Kimmelstiel

Glomerular Changes in Arteriosclerotic Kidney

PLATE 66

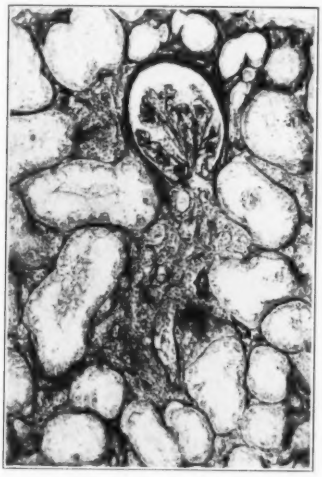
FIG. 7. Capsular thickening associated with tubular atrophy (membrane of tubules delicate). Basement membrane of glomerulus only slightly thickened.

FIG. 8. Glomerulus with thickened basement membrane. Widening of the capsular space due to atrophy of the glomerular tuft.

FIG. 9. Glomerular cyst without capsular thickening.

FIG. 10. Group of glomerular cysts (without thickening of the capsule). Scar tissue towards the medulla.

FIG. 11. Scar with combined ascending and ischemic glomerular atrophy.



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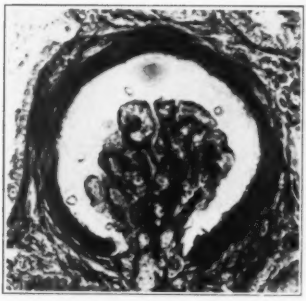

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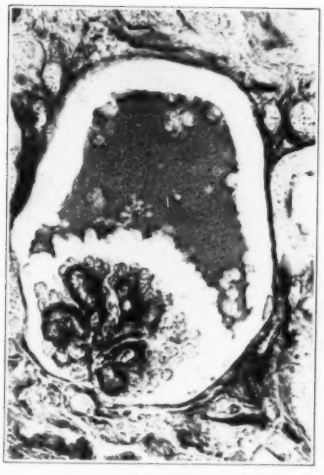

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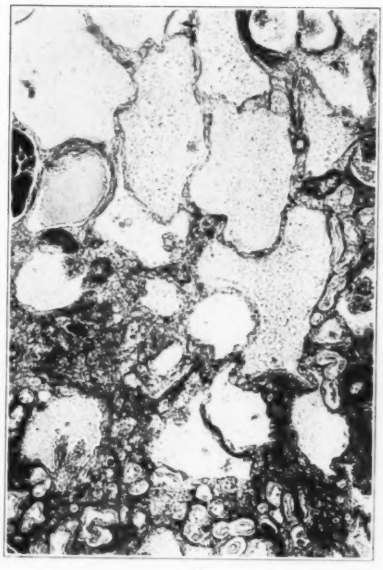

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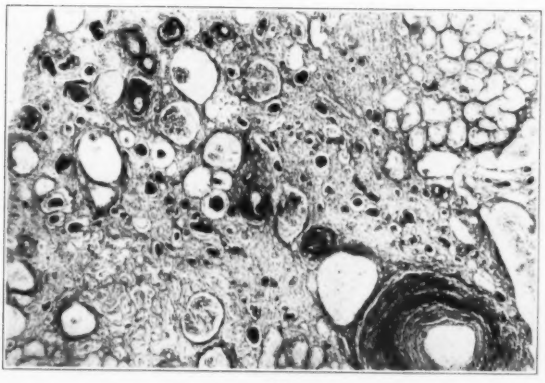

11

REACTION OF PULMONARY TISSUE TO LIPIODOL *

R. Douglas Wright, M.S.

(From the Department of Pathology, University of Melbourne, Melbourne, Australia)

The reaction of tissues to lipoid substances is of increasing interest. The effect of vitamin D on tissue growth is well known. The local reaction of tissues to fats and fatty acids released from their protein envelopes and chemical unions respectively has been discussed by King,[1] Cohen,[2] Lee and Adair,[3] and Stulz and Fontaine,[4] and a simple phagocytosis by local connective tissue and wandering cells has been found. In the case of olive oil containing carotin injected into the peritoneum, Connor[5] found a "foreign body" granuloma to be formed.

Sabin and co-workers[6,7] have demonstrated that tuberculophosphatide gives rise to an epithelioid reaction with Langhans' giant cells and marked caseation: in the environs lymphocytic and plasma cell collections occur. To phthioic acid a reaction more closely resembling the exudative type of tuberculous reaction was found.

Olive oil was found by Sabin[6] to excite a "marked irritation" of the fibrous tissue. White[8] found that when injected subcutaneously in the back of rabbits oleic acid gives rise to a cyst which becomes lined by squamous epithelium if it approaches skin appendages. When the injection is made into the mammary gland metaplasia of the epithelium to the squamous type always occurs.

The reaction of tissues to rapeseed oil containing a 35 per cent iodine is therefore of interest. Such reaction was found in the material here described. It was impossible to retain the lipiodol in the lungs of experimental animals so it could not be determined whether the iodine or the oil was the stimulus to the reaction found.

As no reference could be found in the literature to this type of reaction it is considered worthy of report.

Lipiodol injected into bronchi is usually expelled before any reactive changes to it are set up in the lung. In the lung of a patient into whose bronchi lipiodol had been instilled 12 months previously the oil was retained. At the time of introduction one of the main lateral

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branches of the right bronchus was seen to be blocked completely but the lipiodol passed readily into the lower branches. Roentgenograms taken a week before death showed the lipiodol still to be present in bronchiectatic cavities in the neighbourhood of a relatively radiopaque mass, especially in parts caudal thereto (Fig. 2). Figure 1 shows the manner in which this "trapping" of the lipiodol had taken place. Occlusion of the main bronchus had occurred by the growth of an epithelioma of a lateral branch of the right bronchus. The growth of this mass cranially probably explains the presence of lipiodol in the bronchi above the tumor.

The lungs were removed with the mediastinum. The right lung was adherent to the parietes over its whole surface but more firmly over the lower lobe. The diaphragm was separated from the lung with extreme difficulty when it was seen that this surface of the lung was covered with a thick white tissue. On section this was mainly distributed toward the mediastinum where it was almost an inch thick (2 cm.) but only 0.5 cm. thick at the lateral portions. The surface of this tissue was grey and shining; no fluid exuded from it. The texture was homogeneous, the consistence was harder than mucoid tissue and softer than cartilage. It was very firm and elastic.

The cut surface presented a large, rounded epidermoid carcinoma of a lateral branch of the main bronchus growing in a massive manner into the lung and main bronchus. No metastases were present in the mediastinal glands. The lung parenchyma about this tumor was compressed and fibrous. In the lower portion of the lobe it was not compressed but presented no evidence of alveolar structure on macroscopic observation. Throughout there were lobulated areas of fawn-colored material which stood out in marked contrast to the deep reddish brown of the parenchyma. These masses varied in size from a few mm. to 1 cm. in cross-section. The edges of these areas were definite but slightly blurred. The central zone was essentially homogeneous. The most noticeable feature of these areas was the regularity of distribution and of lobulation in them. The main bronchi were dilated, the mucosa rough and reddened. Blood vessels stood open in the neighbourhood of the tumour.

Frozen sections were taken to include the diaphragmatic surface and the lung with several of the buff-colored areas adjoining it. These were stained with Sudan III which stained the lipiodol deep red. The sections were then stained with haematoxylin.

No fat occurs normally in these areas so that all the material stained by the Sudan III can be interpreted as abnormal. This material can be freed with a needle from the section; it is then seen to be in the form of liquid oil droplets. The areas are, to judge from the roentgenogram taken before death, radiopaque. On this evidence then I will assume that the substance stained by the Sudan III in these sections is lipiodol.

These areas are represented in Figure 4 and Figure 5. The red oil droplets are represented deep black, a green filter and orthochromatic plates being used. In Figure 5 the edges of the two areas of lipiodol accumulation are seen. The lipiodol is in more or less confluent droplets, forming a dense reticulated mass. In Figure 4 these masses are seen to run over many cell areas and are not actually enclosed by any one cell. At A, however, very fine droplets are seen to be included in a macrophage.

When the lipiodol is removed by a fat solvent and the section counterstained by eosin the areas where the lipiodol occurred are seen to be made up of a lace-work of finely reticulated cells with small round nuclei (Fig. 3). The cytoplasm is extremely scanty, slightly vacuolated and extending in fine interconnecting strands from one cell to the other. No collagen fibrils (Van Gieson) were demonstrated arising from these cells.

The lipiodol appears to be enclosed in a foam of cellular syncytium. The origin of these cells is probably the supporting tissue of the bronchi.

Between these areas the remnants of lung parenchyma are seen as small channels with thick fibrous walls.

No bronchi or epithelium are found. The whole of the lobe is remarkably avascular. Even in a section vessels are rarely seen.

The thick hyaline tissue on the diaphragmatic pleural surface is a peculiar form of granulation tissue (Fig. 6). Small, well developed capillaries are seen running at right angles to the lung surface. They are widely separated by a material which takes the eosin poorly, but Van Gieson's stain shows a fine collagenous reticulum. It does not take stains for mucus (thionine and Mayer's mucicarmine) at all. There was no selective staining by iodine or gentian violet. Scattered through it are macrophages in small numbers. Some of these contain small droplets of lipiodol. Most of this substance is, however, extracellular and is almost entirely close to the capillaries in fine

droplets. To liberate them from this situation it is necessary to tear the tissue with needles; they could not have been deposited here during the preparation of the section. Such tissue is unique as far as can be determined from the literature. That it is a reaction to the lipiodol appears probable.

The two outstanding features of this specimen are the reaction of the reticular tissue of the lung to the prolonged presence of lipiodol and the reaction of the pleural tissue.

The cavities which were demonstrated in the first roentgenogram were still diagnosed as such 12 months later. In the meantime they had, however, become completely obliterated and sterile, as judged by staining. This result is certainly due to a tissue reaction to lipiodol which has been retained a long time. The relationship to lipiodol of the peculiar pleural reaction is one of probability only. However, the occurrence of lipiodol in the tissue and the most unusual type of this tissue make the probability great.

Summary

The reaction to lipiodol retained for long periods in the bronchi is the development of lipophages from the supporting connective tissues. No epithelial reaction occurs.

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DESCRIPTION OF PLATE

PLATE 67

FIG. 1. Coronal section through right lower lobe. An epithelioma is growing into the right main bronchus which is dilated. Lobulated masses of lipiodol and the pleural reaction may be seen on the cut surface.

FIG. 2. Roentgenogram of chest 1 week before death, showing opaque circular mass of tumor and presence of lipiodol still present in bronchi.

FIG. 3. The reticulated cells left after dissolving lipiodol from the lung. The openness of the cytoplasmic mesh is well shown. Haematoxylin and eosin stain. × 160.

FIG. 4. Lipiodol in relation to cells is shown. For the greater part it extends in masses over several cell areas but at A it is present as droplets in a macrophage. Sudan III and haematoxylin stain. × 400.

FIG. 5. The edges of two lipiodol masses. Sudan III and haematoxylin stain. × 40.

FIG. 6. Section of pleural reaction tissue. Stained with haematoxylin and Van Gieson. The reticulation of collagen fibres is shown, although these do not stain with eosin. Macrophages and capillaries are also evident. × 160.

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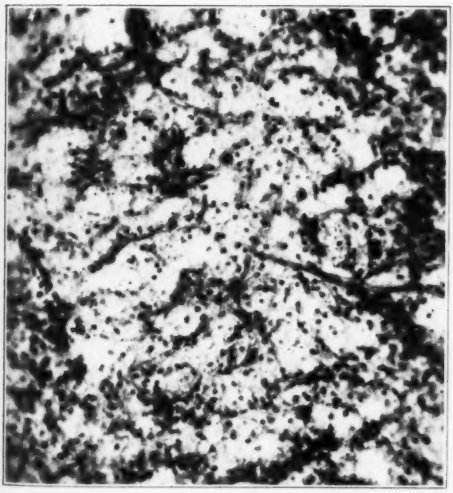

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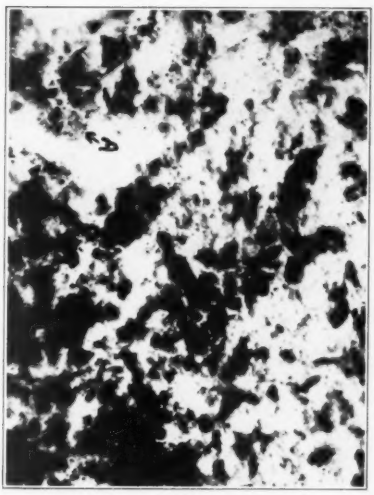

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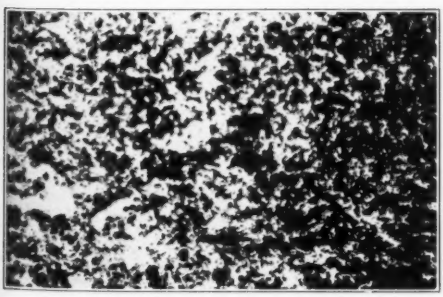

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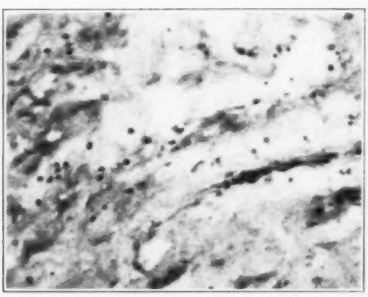

6

Wright

Reaction of Pulmonary Tissue to Lipiodol

INFARCTION OF THE LIVER *

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True infarcts of the liver are so uncommon and the mechanism of their production is, for the most part, so poorly understood that a complete description of 2 additional cases of infarction of the liver seems warranted. Winternitz in 3500 autopsies at Johns Hopkins Hospital did not encounter a single case, Chiari saw 2 cases in 21 years, and many pathologists of wide experience have never seen a case. In a series of about 23,000 autopsies at the University of Minnesota there are but 2 cases.

The infrequency of infarction of the liver intrigued early pathologists. Von Recklinghausen suggested that the double blood supply of the liver was in some way responsible. Following him a number of authors such as Rattone and Mondino, Osler, and Leusden, on the basis of both pathological and anatomical findings and experiments, declared that simultaneous occlusion of both the hepatic artery and the portal vein was necessary to produce true infarction of the liver. This view gained such a firm foothold that it has not been shaken, despite the evidence to the contrary which has accumulated in the past 40 or more years.

The first insight into the true mechanism of infarction of the liver came as a result of the work of the early experimental physiologists. Simon de Metz in 1828 ligated the hepatic arteries in pigeons. He noted that there was no disturbance of the secretion of bile after cutting off the arterial supply of the liver, but he said nothing of necrosis of the liver. In 1857 Kottmeier ligated the hepatic arteries of frogs and rabbits. In frogs there resulted fatty degeneration of the liver; in rabbits he found light yellow, soft areas scattered through the parenchyma of the liver. However, he maintained that these areas of softening were not necessarily produced by the ligation of the liver arteries since he found similar areas in the liver of an animal with a normal arterial circulation.

* Received for publication October 11, 1934.

TABLE I

Cases of Ligation of the Hepatic Artery (or of its Branches) with Infarction of the Liver

Author	Date	Sex	Age	Vessel	Cause of ligation	Pathological lesions in liver
			yrs.			
Kehr, H.	1903	M	29	Main hepatic artery	For aneurysm of right hepatic branch	Necrosis of right border of liver
Beresnegowski, N.	1906	F	46	Right hepatic artery	Bleeding during resection of carcinoma of gall-bladder	Total necrosis of right half of liver
Guibé, and Herrenschmidt, A.	1907	F	22	Left hepatic artery; left branch portal vein	Resection of hydatid cyst left lobe liver	Total necrosis of left lobe
Narath, A.	1909	F	46	Left hepatic artery	Resection of chronic gastric ulcer	Widespread necrosis of left lobe
Kehr, H.	1909	F	36	Hepatic artery proper	During cholecystectomy and removal of common bile duct stone	Necrotic tissue removed on eighth day
Versé, M.	1909	F	48	Main hepatic artery	Resection of carcinoma of stomach	Widespread early ischemic infarction
Wendel, W.	1911			Hepatic artery beyond right gastric	Resection of carcinoma of stomach	Almost total necrosis of liver and gall-bladder
Wilms, M.	1912	M	47	Branch of hepatic artery (ligature?)	Resection of carcinoma of stomach	Extensive necrosis of left lobe
Schütz, H.	1914	M	48	2 branches of hepatic artery	Resection of carcinoma of stomach	Almost total necrosis of left lobe
Kretz, R.	1916			Right hepatic artery	During an operation	Necrosis of two-thirds of liver

Holst, S. F.	1920	M	66	Main hepatic artery	Resection of carcinoma of stomach	Left lobe small, soft, with areas of necrosis
Ritter, A.	1922	M		Right hepatic artery	Resection of carcinoma of stomach	Necrosis of right lobe of liver
Newcomb, W. D.	1930			Hepatic artery	Operation	Central necrosis of each liver lobule
Gerlach, W.	1930	F	30	Right hepatic artery	For severe bleeding after cholecystectomy	Numerous areas of necrosis
Graham, R. R., and Cannell, D.	1933	M	49	Main hepatic artery	Resection of carcinoma of stomach	Multiple necrotic areas in left lobe
Shann, H., and Fradkin, W. Z.	1933	F	48	Hepatic branches (?)	During cholecystectomy	Grayish-white mass 10 x 5 cm. sequestered
Kerr, R. W.	1933	F	57	Right hepatic artery. Portal vein	During cholecystectomy	Massive infarction of right lobe

Postoperative Infarction of Liver not due to Ligation of Hepatic Artery

Kausch	1904	F		A large branch of hepatic artery	Thrombosis during cholecystectomy	Slight necrosis of liver
Cioni, C.	1932	M	49	Left hepatic artery	Thrombosis following gastroenterostomy	Anemic infarction of left lobe

Betz (1863) in his experiments on dogs came to the conclusion that ligation of the common hepatic artery at its origin from the celiac was not dangerous. If, however, the artery was tied beyond the origin of the pancreaticoduodenal branch, fatty degeneration of the liver was present after 48 hours. In 1876 Cohnheim and Litten ligated all the arterial vessels present in the hepatoduodenal ligaments of rabbits. There resulted a total necrosis of the liver. The tying of only one branch of the hepatic artery resulted in necrosis of the corresponding lobe alone. Following this, Litten (1890), Pick (1890), De Dominicis (1891), Hahn and co-workers (1893), Janson (1895), Doyon and Dufourt (1898), Dujarier and Castaigne (1899), Ehrhardt (1902), Tischner (1904) and others investigated this problem in various animals with widely varying results and even more diverse interpretations.

It remained for von Haberer (1906) to clarify the subject. This investigator ligated the hepatic arteries of dogs, cats and rabbits. He injected a colored mass into the blood vessels after sacrificing the experimental animals in order to trace the vessels to the liver more readily. In this way he was able to establish that in those animals that did not die in a short time, the liver received its arterial blood from some source other than the hepatic artery. He performed several types of ligation: of the common hepatic artery as close to the celiac axis as possible, of the main hepatic artery distal to the origin of the right gastric, and of the right gastric and the gastroduodenal with resection of the arterial system between the ligatures. In a few cases the animals survived even the last procedure, and in these it was possible to demonstrate markedly developed diaphragmatic arteries. If the arterial supply was actually cut off, the animal promptly died of necrosis of the liver.

Many workers subsequently reinvestigated this problem in a large variety of animals (Bainbridge and Leathes, 1907; Nicolleti, 1910; Whipple and Sperry, 1909; Steckelmacher, 1913; Behrend, Radasch and Kershner, 1922; Loeffler, 1927; and others).

Of the recent studies, that of Cameron and Mayes (1930) deserves special mention. These investigators ligated the hepatic arteries of rabbits at various sites. They were able to corroborate the finding of necrosis of the liver following ligation of the main hepatic trunk. In addition they studied microscopically, as well as in gross, the stages in the development of the necrosis in the livers of their animals.

They were able to demonstrate definite necrosis in about 15 hours. The necrosis was usually massive and affected all zones of the liver lobules uniformly. A striking feature of their study was the relative immunity of the bile ducts and of the other structures within the portal canals from the necrotic process. Thrombi, particularly within the venous branches, were frequent, but by no means a constant finding.

There is evidence similar in nature to that described in experimental animals for the pathogenesis of infarction of the liver in man. Accidental ligation of the hepatic artery or of one of its branches, and purposeful ligation of the artery, chiefly for aneurysms, have provided us with a good insight into the importance of the hepatic arterial supply for the liver of man, as well as with most of the recorded cases of infarction of the liver.

I have been able to collect only 42 such cases from the literature. That they are more common is indicated in the opinion expressed by Behrend (1920) that "some unexplainable deaths following the operation of cholecystectomy may be due to ligation of the hepatic artery."

Kehr in 1903 ligated the main hepatic artery for an aneurysm of its right branch. The right border of the liver became necrotic and a strip 2 cm. wide ultimately separated. The patient recovered. Beresnegowski (1906) reported a case in which Tichow ligated the right branch of the hepatic artery during the course of an operation for carcinoma of the gall-bladder. There followed a total necrosis of the right half of the liver with death of the patient in 72 hours. Guibé and Herrenschmidt (1907), Narath (1909), Wendel (1911), Wilms (1912), Kretz (1916), Holst (1920), Ritter (1922), Gerlach (1930), Newcomb (1930), Graham and Cannell (1933) and Kerr (1933) report cases of ligation of the main hepatic artery or of one or more of its primary branches during the course of operation, with more or less complete infarction of the liver. Descriptions vary from those of multiple, anemic, sharply circumscribed areas of necrosis to total necrosis of the liver. This seems to prove that interruption of the arterial supply to the liver produces infarction. But how are we to explain the cases of ligation of the hepatic artery in man with recovery? Palacio (1898), Kehr (1903, 1909, 1913), Bakes (1904), Alessandri (1908), von Haberer (1909), Wendel (1911), Friedman (1912), Bertram (1913), Anderson (1919), Käding (1919), Ritter (1922),

Smith (1921), von Hofmeister (1922), and Shann and Fradkin (1933) all have reported cases of ligation of the hepatic artery or of its main branches with recovery of the patient.

On critical examination these cases fall into three groups. The first includes the cases of Palacio, Wendel and von Haberer, who ligated one branch of the hepatic artery preparatory to removal of the corresponding lobe of the liver. Obviously no necrosis could be expected in these cases. The second group comprises cases in which the hepatic artery or one of its branches was ligated during the course of some operative procedure in the upper abdomen (cholecystectomy, gastric resection, and so on). Of these the main hepatic arteries were ligated in only 2 cases (Ritter, 1922, and von Hofmeister, 1922). In the others a branch or branches of the hepatic artery were ligated. The possibility of anomalous branches could not be ruled out in these cases since the patients recovered. The third group includes the cases in which the hepatic artery or its branches were ligated in the removal of an aneurysm. Of these again only two involved ligation of the main hepatic artery (Kehr, 1903, and Käding, 1919). In this group there exists, too, the possibility of anomalous hepatic vessels. Moreover, particularly in the aneurysmal group, because of the relatively slow obstruction of the hepatic vessels, it is probable, as Segall has shown, that a collateral circulation is established especially with the diaphragmatic arteries, but also in part with the artery of the ligamentum teres, the right gastric or gastroduodenal arteries, or with arteries in adhesions between the abdominal viscera and the liver capsule. Cameron and Mayes (1930) have shown that in the rabbit methylene blue injected into the right internal jugular vein stains the liver even after the structures in the hepatoduodenal ligament and the hepatic veins are tied off. The collateral circulation responsible for the staining they conclude "is an important factor in maintaining the life of considerable parts of the liver after complete obstruction of the hepatic artery."

Narath and Ritter, on the basis of their experience with ligation of the hepatic artery or of its branches in humans, and Segall upon the basis of his studies of injected specimens of human livers, agree that the rules of surgical ligation established by von Haberer on experimental animals are valid for man.

Narath stated these rules as follows:

(1) The ligation of the main hepatic trunk is permitted providing at least one collateral is uninjured.

(2) The ligation of the hepatic artery proper before the origin of the right gastric artery is permitted if necessary. It may produce small areas of liver necrosis.

(3) The ligation of the hepatic artery proper is not permitted because of the great danger of liver necrosis. Exception — peripheral aneurysms.

(4) The ligature of a branch of the hepatic artery is not permitted, especially in patients with weak hearts.

We may conclude from these observations that infarction of the liver is produced in man by cutting off the arterial supply, just as has been amply demonstrated in experimental animals.

Let us examine now the group of cases in which infarction of the liver has occurred spontaneously, leastwise in the absence of any operative interference. Omitted from consideration here is the group that has been called "pseudoinfarcts." This includes cases of necrosis of the liver following injury. In these, as Zimmerman (1930) points out, there always exists the possibility that the necrosis of the liver cells is the direct result of the trauma. The so-called "atrophic red infarcts" which occasionally follow thrombosis of the portal vein have also been omitted because these have been shown to be due to atrophy and not to true necrosis. Finally, all cases of necrosis caused by thrombosis of the portal radicles have been omitted; first, because the mechanism of their production is quite different from that of the group under consideration; and second because, as Chiari pointed out long ago, the microscopic picture resulting from such thrombosis is quite different from that following interruption of the hepatic arterial supply.

I have been able to collect from the literature 52 cases that fulfill the essential requirements of anemic infarction of the liver. In these 52 cases the etiological factors may be divided as follows:

(1) Embolism of hepatic artery.	
(*a*) subacute bacterial endocarditis	13
(*b*) mural thrombus	4
(*c*) paradoxical embolism	2
(*d*) thrombus in an aneurysm	2
Total embolic	21
(2) Periarteritis nodosa of branches of hepatic artery	22
(3) Thrombosis of hepatic artery (three in aneurysms)	6
(4) Endarteritis of hepatic artery	2
(5) Hypoplasia of hepatic artery	1

TABLE II

Cases of Infarction of Liver (Not Including Periarteritis Nodosa)

Author	Date	Sex	Age	Mechanism of infarction	Pathological lesions in liver
			yrs.		
Ross, G., and Osler, W.	1877	M	21	Thrombus in aneurysm at bifurcation of hepatic artery	Numerous areas of necrosis with subsequent abscess formation
Obermüller, J.	1886	F	60	Thrombosis of multiple aneurysms of small branches of the hepatic artery	Multiple anemic infarcts
Orth, J.	1887			"Endocarditis diphtheroides" with emboli to the liver	Faint yellowish, round infarct surrounded by a bright red zone
Rattone, G.	1888	F	young	Endocarditis secondary to puerperal sepsis with emboli to the liver	A small reddish brown infarct
Rattone, G.	1888	M	66	Obliterative endarteritis and thrombosis of hepatic branches; thrombosis of branches, portal vein	Two small "hemorrhagic" infarcts
Köhler, B.	1891	M	20	Ulcerative endocarditis; embolus in branch of hepatic artery	Multiple abscesses and a zone of necrosis
Ogle, C.	1895			Embolus from aortic valve blocking hepatic artery at its bifurcation	Multiple buff-colored infarcts from size of pea to hazelnut
Chiari, H.	1898	F	52	Mitral endocarditis. Embolus in hepatic artery beyond right gastric	Complete necrosis of liver
Chiari, H.	1898	F	27	Mitral endocarditis. Emboli in smaller branches of hepatic artery	Multiple infarcts, some as large as a hazelnut
Castaigne, J.	1899			Cardiac thrombus; multiple emboli to liver	"Hemorrhagic" infarction of liver
Brion, A.	1901	M	15	Four intrahepatic aneurysms	Necrotic areas in the liver
Baldwin, F. A.	1902	M	39	Mural thrombus in left auricle	Multiple anemic infarcts
Ruczyński, B.	1905	F	40	Mural thrombus of right ventricle; patent foramen ovale; emboli in hepatic artery	Multiple zones of liver necrosis
Sotti, G.	1906	F	67	Aortic endocarditis. Thrombosis of portal vein and hepatic artery	"Hemorrhagic" infarction of left lobe and part of right

Reichmann	1908	M	26	Multiple emboli from a thrombosed aneurysm on main hepatic artery	Multiple infarcts of liver; many show cavity formation
Versé, M.	1909	F	26	Thrombosis central and hepatic veins with extension into hepatic artery and portal vein	Anemic infarcts in areas not involved by "more extensive process"
Herrmann, A.	1910		76	Thrombosis of branch of hepatic artery	A yellowish white dry area in right lobe
Dean, G., and Falconer, A. W.	1912	M	22	Aneurysm of hepatic artery, chiefly right branch	Two-thirds of right lobe necrotic; few cyst-like cavities in necrotic areas
Schütz, H.	1914	F	22	Aortic endocarditis; emboli to liver	Yellowish brown area of necrosis size of a hazelnut
Kretz, R.	1916	M	30	Acute endocarditis	Six anemic infarcts of liver
Wiessner, J. M. P.	1917	M	56	Mural thrombus in aorta with embolism to medium sized branches of hepatic artery	Multiple yellowish areas of necrosis, some as large as a walnut
Askanazy, M.	1918	F	71	Mural thrombus of aorta (?) with embolism of anomalous hepatic artery	Multiple anemic infarcts of liver
Mittasch, G..	1924	M	61	Emboli from auricular thrombi and possibly from mitral valve	Multiple "hemorrhagic" infarcts
Orlandi, N.	1924	F	26	Chronic mitral disease; mural thrombi in left auricle and ventricle with emboli to liver	Numerous grayish infarcts in right lobe
Orlandi, N.	1924	M	36	Embolism of hepatic arteries from bacterial vegetations on aortic valve	Multiple necrotic areas in both lobes
Orlandi, N.	1924	F	16	Thromboendarteritis with mycotic aneurysms of hepatic arterial branches	Multiple anemic infarcts
Hampeln, P.	1924	M	55	Infectious thrombosis of hepatic artery and its branches	Multiple infarcts of liver
Gerlach, W.	1930			Paradoxical embolism following thrombosis of femoral and iliac veins, and lower vena cava	Infarction of lower part of right lobe
Zimmerman, H. M.	1930	F	31 hrs.	Hypoplasia of hepatic artery; thrombosis of portal vein	Infarction of left lobe
Cioni, C.	1932	F	49	Recent ulcerative endocarditis of mitral and tricuspid valves; mural thrombosis of left atrium. Embolism of right hepatic	Infarction of right lobe
Pass	1934	M	24	Compression of main hepatic artery by extension from carcinoma of stomach	Multiple areas of infarction

The most common single cause of infarction of the liver, at least in the cases reported, is evidently periarteritis nodosa of the branches of the hepatic artery. In 170 case reports available, of the approximately 200 cases of periarteritis nodosa reported in the literature, there were found 22 cases of infarction of the liver.

In a few cases there was a concomitant endophlebitis or thrombosis of the portal vein or of its radicles. These cases would tend to support the contention of Rattone and Mondino, Leusden and Osler that occlusion of both the hepatic artery and the portal vein was required to produce infarction of the liver, were there not many more cases reported in which the arterial supply of the liver alone was disturbed.

Some authors, notably Wiessner (1917), have assumed that infarction of the liver following occlusion of the hepatic artery occurs only after necrosis and thrombosis of the portal venules with cutting off of the portal venous flow as well as of the hepatic arterial supply. Loeffler (1927) has recently reopened the whole controversy as to the relative importance and function of the hepatic arterial and of the portal venous supplies to the liver by stating that the hepatic arterial blood supplies the bile ducts and the walls of the portal venous radicles alone and that necrosis of the liver cells following occlusion of the hepatic artery is, therefore, really the sequel to necrosis of the bile ducts and of the portal vein.

However, it has been estimated that 35 per cent of the blood of the liver is supplied by the hepatic arteries, whereas the structures of Glisson's capsule constitute at most 10 per cent of the liver substance (Pfuhl, 1932). Furthermore, whereas the liver constitutes only 3 per cent of the body weight, it receives 5.1 per cent of the aortic blood through the hepatic arteries alone. Moreover, experiments with the Eck fistula have shown that the hepatic artery alone can supply the entire demand of the liver. These facts plus the observations of Cameron and Mayes of the relative immunity of the portal canals in necrosis of the liver following experimental ligation of the hepatic artery in animals, render it probable that the hepatic arterial blood takes part directly in the supply of the liver lobules.

That the portal vein plays a relatively minor rôle in the supply of the liver has been appreciated by some for many years. Many workers have reported accidental finding of completely thrombosed portal veins at autopsy, and the experimental work, although not altogether

unequivocal, nevertheless indicates that ligation of the portal vein in experimental animals is usually uneventful. Even simple atrophy of the liver or so-called "atrophic red infarcts" follow obstruction of the portal vein only when there is a concomitant impairment of the arterial circulation, as in a general heart failure. Hence, one would not expect the portal venous supply to be a very important factor either in the causation or in the prevention of necrosis of the liver.

TABLE III

Cases of Infarction of Liver with Periarteritis Nodosa of Hepatic Branches

Author	Date	Sex	Age	Pathological lesions in liver
			yrs.	
Mönckeberg, J. G.	1905	M	18	Several brownish, irregular infarcts
Versé, M.	1907	M	33	Multiple infarcts
Longcope, W. T.	1908	M	35	Multiple infarcts
Versé, M.	1909	F	19	Multiple anemic infarcts
Cameron, H. C., and Laidlow, P. P.	1918	M	27	A white infarct 4 x 3 cm. in left lobe
Kroetz, C.	1921	M	39	Multiple infarcts
Marinesco, M. G.	1923	M	28	Multiple small areas of necrosis
Pol	1925	F	23	Anemic infarcts
Baló, J.	1926	M	23	Recent and old infarcts
Christeller, E.	1926	F	29	Numerous anemic infarcts
Christeller, E.	1926	M	31	Anemic infarcts, chiefly subcapsular
Harbitz, F.	1927	M	32	Irregularly distributed areas of necrosis
Weigeldt, W.	1927	M	39	Anemic infarcts
Blum, K.	1929	M	43	Multiple infarcts
Arkin, A.	1930	M	55	Dark red depressed areas consisting of necrotic liver parenchyma
Arkin, A.	1930	M	50	Numerous, irregular, dark red infarcts
Arkin, A.	1930	M	34	Numerous gray-red infarcts
Arkin, A.	1930	M		Liver looks like syphilitic hepar lobatum (healed infarcts?)
Vance, B. M., and Graham, J. E.	1931	M	21	Multiple wedge-shaped anemic infarcts
Jäger, E.	1933	M	39	Anemic infarcts
Pass	1935	M	27	Multiple infarcts

Although we have demonstrated that the process of infarction is the same in the liver as in the spleen or kidneys, we have not shown why it is so rare in the liver. There are four observations that may help account for its rarity. The first is that the arrangement of the hepatic arterial supply is such that it renders embolism of the liver unusually difficult. The hepatic artery describes an arc of about 180° in its course to the liver. Askanazy was so impressed with the protective property of the peculiar vascular course that, finding a

case of embolism of the hepatic artery with infarction of the liver, he carefully dissected out the artery and was able to prove that it arose in his case from the aorta and passed directly to the hilum of the liver. Perhaps similar anomalies might have been found in some of the other cases of embolism of the hepatic arteries had careful examination of these vessels been made.

The second fact is that, as we have pointed out above, a collateral circulation protects the liver.

A third is the observation of Chandler (1920), who noted that the liver cells of dogs withstood surprisingly well the temporary anemia (3–12 hours) following ligation of both the hepatic artery and the portal vein. Even after 12 hours there was no necrosis of liver cells, but there was a marked fatty degeneration of the central half of the liver lobules. He concluded that "this power of the hepatic cells to resist local anemia probably accounts for the infrequency of infarcts in the liver." We must not examine this experiment too critically, however, for we are likely to discount its significance on the basis of a probable collateral arterial supply.

The final fact is that, as Cameron and Mayes have shown experimentally, infarcts of the liver frequently become converted into abscesses. The pathologist confronted at autopsy with multiple abscesses of the liver cannot know that these have earlier been infarcts.

There are a few cases reported which may conceivably represent healed infarcts of the liver. These include such cases as that of Ledieu who found an aneurysm the size of a hazelnut on the main trunk of the hepatic artery. The aneurysmal cavity was occluded by a firm clot. The liver showed cirrhosis. The increased fibrous tissue in this case might represent scars of healed infarcts (see Cameron and Mayes). Arkin reports a case of healed periarteritis nodosa with a small liver resembling a syphilitic hepar lobatum evidently produced by healing of infarcts. Cases of this kind are, however, for the most part so difficult to interpret, particularly in the absence of careful microscopic reports, that I shall dismiss this group without further mention.

Finally I wish to add 2 cases of multiple anemic infarcts of the liver.

Case Reports

Case 1. The patient, a white male aged 27 years, was admitted to the hospital on March 8, 1924, complaining of moderate pain in the abdomen, shifting in character, pain in the back and legs, and weakness. One month previously while helping to lift a heavy log, he had slipped and had had to use all of his strength to keep from falling. At that time he experienced a sudden severe pain in the abdomen, which confined him to bed. He had found it necessary to stay in bed since, because of pain and some vomiting.

He had never been ill before except for an infection of the left hand in November, 1923. There was no history of any venereal disease. For the two months just preceding his illness he had been working in a logging camp.

On physical examination his tongue was moderately coated, his teeth poor. The heart and lungs were normal. There was some tenderness in the epigastrium and in the left lumbar region on deep pressure. The entire abdomen was tympanitic with the exception of the left lumbar region which was dull. There seemed to be a slightly increased resistance to pressure in the left lumbar region, but the abdomen was otherwise soft.

Laboratory examination on March 9 showed: urine — amber color, acid, specific gravity 1010, negative for albumin and sugar. The leukocyte count on March 11 was 30,000.

The patient vomited several times after admission to the hospital. The abdominal pain shifted from one side of the abdomen to the other and was so severe that it required morphine for relief.

On March 15, 1924, a laparotomy was performed. Only a small amount of dark bloody fluid was obtained, but no lesion could be demonstrated. Drains were inserted and the wound was closed.

The patient expired on March 26, 1924. His temperature on admission was 101° F. It varied between 97 and 101 during his hospital stay. Clinically it was felt that the patient had had an intestinal hemorrhage.

Autopsy Report

The body was that of a poorly nourished, adult male. A rather recent, almost completely healed surgical incision extending from the umbilicus to the symphysis pubis was present. Rigor was present. There was no edema. A distinct bluish discoloration was seen over the chest and abdomen.

The omentum was brownish green and was attached by soft adhesions to the hepatic flexure of the colon. A small white nodule just lateral to the hepatic flexure was observed. The posterior abdominal wall on the left was pushed forward by a large hematoma. There were a number of soft adhesions between the coils of small intestine and the sigmoid colon, as well as between the transverse colon and the liver.

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The spleen contained several white infarcts, varying in size from 0.5 to 1 cm. in diameter.

The stomach contained 200 cc. of thin fluid containing coffee-ground-like material. Four ulcers were found on its lesser curvature, the largest estimated to be 3.5 by 2 cm. The other ulcers were 5 to 6 mm. in diameter. In the center of the large ulcer was found an open blood vessel. It was about 0.5 mm. in diameter and was opened for a length of 2 mm.

The liver was estimated to weigh 2000 gm. The surface was bluish red. It contained numerous, irregularly shaped depressed areas, and one light brown, soft area in the dome about 2 cm. in diameter. On section the liver showed numerous infarcts of different sizes and shapes. One large infarct was red and the vessel supplying this region was closed by a small red plug. Most of the other infarcts were white but some contained a thick brownish fluid.

The right pleural sac contained about 100 cc. of dark, thin fluid; the left contained no excess of fluid. There were many firm adhesions between the lungs and the diaphragm.

The pericardial lining was smooth and shining. The sac contained about 20 cc. of blood-stained fluid. There were numerous nodules along the vessels in the heart wall. These were hard, whitish in color and were surrounded by small red zones. There was no embolus in the pulmonary artery. The heart muscle appeared light red in color; that of the left ventricle appeared somewhat thicker than normal. The estimated weight of the heart was 400 gm. The mural and valvular endocardium appeared normal.

On section the lungs showed a slight edema but were otherwise normal.

The kidney capsules stripped easily. Numerous yellowish spots were scattered over the surfaces of both kidneys. On section the right kidney showed numerous infarcts, most of which were white. Some showed reddish zones about the necrotic centers. The left kidney was surrounded by a very large hematoma extending from the diaphragm to the pelvic brim and from the lateral abdominal wall over the midline. This hematoma was entirely within the kidney capsule. On the anterior surface of this kidney was a perforation in the cortex measuring about 5 mm. in diameter which led into a small blood-filled cavity in the cortex. Numerous white infarcts were present in this kidney.

The aorta was smooth throughout its length. The adrenals were not examined.

Anatomical Diagnoses: Periarteritis nodosa; multiple infarcts of kidneys, spleen, liver and stomach wall; hemorrhage from left kidney; hemorrhage from ulcer of stomach.

Microscopic Examination

Microscopic examination of the kidneys, liver, heart, intestines and spleen reveals a marked involvement of the small arteries. These vessels all show infiltration of the adventitia with polymorphonuclear leukocytes and small lymphocytes. There is a marked hyaline degeneration of the media and a slight proliferation of the intima. Thrombi are present in many of the larger arteries of the kidneys, spleen and liver. A few of the vessels involved, particularly in the spleen and heart, show a marked fibrous proliferation in both the intima and media, and to a lesser degree in the adventitia. In the intestines many areas of necrosis of the mucosa and submucosa can be seen related to the thrombosed vessels. The spleen, kidney and liver all show areas of infarction. In the liver there is complete necrosis of all the tissue elements in the infarcted areas (Fig. 4). These represent true, so-called anemic infarcts of the liver.

Case 2. The patient, a white male, aged 24 years, was evidently well until about November, 1933, when he had an attack of what was called "influenza." He never quite recovered from this attack. He felt weak and began to lose weight.

In February, 1934, a gastro-intestinal barium study disclosed a stenosing lesion at the pyloric end of the stomach, evidently carcinoma. He then developed some jaundice and began to have occult blood in the stools. The hemoglobin fell to 18 per cent. Transfusion was performed and the hemoglobin rose to 40 per cent, at which level it stayed to the end, despite constant slight bleeding into the bowel. He developed severe abdominal pains and attacks of vomiting, both of which were controlled to some degree by pantopon. The blood pressure was 130/80. The heart was normal, the lungs were clear. The liver seemed enlarged and irregular. The spleen was not palpable. There was constantly moderate to marked distention of the abdomen. The patient was put on a liquid diet but terminally could retain nothing taken by mouth but Vichy water.

During the last 2½ weeks of life he ran an elevated temperature, up to 101.5° F. The chest remained clear. The jaundice became progressively more intense.

The urine upon one occasion showed a specific gravity of 1024, acid reaction, trace of albumin, negative sugar, occasional red and white cells, 4 plus bilirubin, but no urobilinogen. The stools constantly showed 4 plus occult blood but were never frankly tarry. The patient evidently died of inanition.

Autopsy Report

The body was well developed but extremely emaciated. No edema or cyanosis; jaundice Grade 4 of the skin and mucous membranes. A hard nodular mass could be palpated in the epigastrium, extending down to within 3 cm. of the umbilicus in the midline; it was evidently not the liver. The autopsy was limited to the abdomen.

About 2000 cc. of clear bile-stained fluid was present in the peritoneal cavity. The nodular mass proved to be a large tumor attached to the greater curvature of the stomach at its pyloric end. The liver was at the rib margin. The appendix was normal. The diaphragm was at the fourth interspace on each side.

The spleen weighed 300 gm. There were several infarcts about 1 cm. in diameter situated just under the capsule. The spleen was congested and was somewhat firmer than normal.

The liver weighed about 1500 gm. It was deep olive green in color and its surface was slightly nodular. On section the elevations proved to be small yellowish areas, which were found to be infarcts (Fig. 1). Greenish, clear bile flowed from the surface of the liver. The gall-bladder, the cystic duct and both hepatic ducts were much dilated. The common bile duct and the hepatic artery were compressed to the point of complete closure by a mass of tumor continuous with that in the stomach (Fig. 2). The anterior wall of the portal vein was infiltrated with tumor but its lumen was patent.

The rugae of the stomach were hypertrophied and the stomach was coated with a layer of fresh blood. At the pyloric end was an ulcer 6 cm. in diameter with a necrotic base and with hard elevated borders. The tumor had penetrated the stomach wall and had infiltrated the head of the pancreas as well as the lesser omentum. It had grown down along the common bile duct and around the ampulla of Vater, which measured 1 by 0.5 cm. and protruded into the lumen of the duodenum (Fig. 3). The rest of the gastro-intestinal tract was normal.

The pancreas was extensively infiltrated by tumor. The parts not involved were firm and fibrous.

The right kidney weighed 125 gm., the left 150 gm. On section they were bile-stained but otherwise normal. The urinary bladder and genital organs were normal.

The aorta was normal. There was a large mass of periaortic lymph nodes, the individual nodes varying from 1 to 2 cm. in diameter.

The head was not examined.

Anatomical Diagnoses: Carcinoma of the pyloric end of the stomach with metastases to the pancreas, periaortic lymph nodes and lesser omentum; obstruction of the common bile duct and hepatic artery; ascites; severe inanition; jaundice; multiple infarcts of the liver and spleen.

Microscopic Examination

Microscopically the tumor of the stomach proves to be a scirrhous carcinoma. The liver shows multiple areas of infarction. These each include from one to several liver lobules. In these areas there is a complete necrosis of the blood vessels and of the connective tissue septa as well as of the liver cords (Fig. 4). No evidence of a predilection for any particular zone of the liver lobule can be observed. Occasional portal venules both within and at the periphery of necrotic areas are thrombosed. The necrotic areas merge gradually at their peripheries with the normal liver tissue. The infarcted areas are surrounded by a few polymorphonuclear and mononuclear cells, but on the whole there is very little cellular reaction to the dead tissue. The peripheral parts of the infarcts are bile-stained. The rest of the liver tissue shows slight atrophy of the liver cords and marked stasis of bile, particularly in the form of bile thrombi.

Because of the unexplained infarcts of the spleen we must admit that, although the occlusion of the hepatic artery seems sufficient to account for the infarction of the liver, a mural thrombus may have been present or a subterminal endocarditis which cast off emboli producing the infarcts in the liver as well as in the spleen. However, because of the lack of embolic phenomena elsewhere and because of the large number of infarcts in the liver we are inclined to discount this possibility.

Summary

A review of the literature of infarction of the liver with a report of 2 additional cases is given.

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DESCRIPTION OF PLATE

PLATE 68

FIG. 1. Case 2. Gross appearance of the infarcts of the liver.

FIG. 2. Case 2. Section through the free margin of the lesser omentum. The arrow points to the hepatic artery surrounded and compressed by a large mass of tumor tissue.

FIG. 3. Case 2. Gross appearance of the carcinoma of the pyloric end of the stomach.

FIG. 4. Case 2. Low power view of an infarct of the liver. Note the nearly complete disintegration of the portal canals as well as of the liver cords in the infarcted area. Similar lesions were abundant in Case 1.

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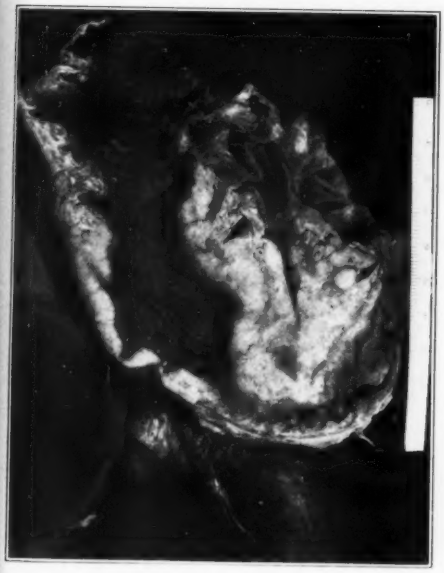

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Pass

Infarction of the Liver

PRIMARY ADENOCARCINOMA OF THE PANCREAS IN A FIFTEEN YEAR OLD BOY *

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REVIEW OF THE LITERATURE

Primary carcinoma of the pancreas in children is rare. Extensive search of the literature revealed the report of relatively few authentic cases. Of those that have been found some were unproved and others were doubtful cases. Inadequate description, incomplete postmortem examinations, use of vague equivocal terms such as "cancer-like induration," absence of microscopic study and confusing case histories make the analysis of these cases difficult. The proved reported cases of primary carcinoma of the pancreas in persons under 20 years of age in the literature are 5 in number.

CASE 1. Bohn,[1] 1885, a 7 months old female infant. The tumor arose in the head of the pancreas with metastases to surrounding lymph nodes and liver. Cytological examination revealed a typical carcinoma simplex.

CASE 2. Kühn,[2] 1887, a 2 year old girl. The head of the pancreas was involved by tumor, as were the neighboring lymph nodes, liver and lungs. Microscopically the tumor was an adenoid cylindrical cell carcinoma.

CASE 3. Simon,[3] 1889, a 13 year old boy. The tumor was "two-fist" sized, involving the head of the pancreas and infiltrating through the mucosa of the duodenum. The tail of the pancreas was relatively uninvolved. The bile ducts were compressed by the tumor with dilatation above. Metastases to liver, surrounding lymph nodes and kidneys were present. No microscopic study was reported.

CASE 4. Kaufmann,[4] 1929, a 19 year old girl. The tumor, which was the size of a bean, arose in the tail of the pancreas, with numerous metastatic nodules in the liver (3300 gm.) and carcinomatosis of the pulmonary lymphatics. Microscopically this was a carcinoma solidum with medium sized cells.

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CASE 5. Stout and Todd,[5] 1932, a 4 year old boy. The head of the pancreas was enlarged and increased in density. The tumor was about 5 cm. in diameter, unencapsulated. It encroached upon but did not involve the duodenum. The neighboring lymph nodes and the liver showed metastases. Microscopically the tumor was an adenocarcinoma, probably arising from the ductal epithelium.

Schamoni,[6] in 1924, mentioned a case of carcinoma of the pancreas in a 16 year old boy. The case was not reported as such but was listed in a statistical study of malignant tumors before and after the World War. No description was given.

Gruber [7] and Merkel [8] cited von Sotow's [9] case in a 1½ year old child, but despite extensive efforts the original case report could not be obtained.

In 1915 Stewart and Stewart [10] reported a carcinoma of the tail of the pancreas in a 9 year old boy. An autopsy, limited to the surgical incision only, was permitted and the data submitted do not allow conclusions as to whether this was a primary or secondary tumor of the pancreas.

Philipp[11] cited cases by Todd, Battersby, Hofmann and von Rokitansky as doubtful, because of inadequate description and because they dated back to times when knowledge of the diseases of the pancreas was unsatisfactory.

In 1818 Todd [12] reported a case of a 14 year old girl who complained of severe upper abdominal pain, with icterus, emaciation and edema of the lower extremities. At autopsy the pancreas was "scirrhous" and the head and surrounding tissues formed a hard solid mass which entirely obliterated the lumen of the distal end of the common bile duct. The proximal portion of the duct formed a huge dilated sac extending from the porta hepatis to the os sacrum. The gall-bladder was not dilated because of a kinking of the cystic duct. No mention was made of metastases. Battersby's [13] case in a 14 year old girl was found to be a reference to Todd's case.

In 1866 Hofmann [14] reported a case in an 8 months old premature infant who lived only a half hour. The placenta was grossly normal. The pancreas was very hard and nodular. The mesenteric lymph nodes were enlarged and nodules were present in the liver. Professor Wedl called this a carcinoma arising in the pancreas. However, the mother had had numerous stillborn children from no apparent

cause. This case was considered doubtful because of the history of probable syphilis and the lack of microscopic confirmation.

In 1842 von Rokitansky [15] mentioned a case of cancerous infiltration of the entire pancreas of a newborn infant, reported by Berg during his stay at von Rokitansky's clinic.

Gruber [7] cited Dutil [16] as having reported a case in 1888 in a 14 year old child, but examination of the original reference revealed the patient to be a 47 year old coach driver.

Oser [17] and Rauschmann [18] attributed a case of primary carcinoma of the pancreas in a 13 year old boy to Bandelier [19] in 1896. However, the case was identical with the one described by Simon, and no doubt was the same case.

Williams [20] stated Israel [21] reported a case in a 13 year old child but this was a carcinoma of the kidney.

Claessen [22] mentioned a case report by Harder of a 14 year old girl in whom the pancreas was found to be of scirrhous hardness and, in the region of the liver, to be of fist-size or larger. On sectioning the pancreas, purulent material flowed out. Abscesses were present in the right lung. Claessen [22] and Wolff [23] thought this case to be extremely doubtful.

Rauschmann [18] cited a case by Cruveilhier [24] in a stillborn male infant and Williams [20] listed Arnozan [25] as reporting a "so-called congenital cancer." The original articles could not be found.

A sixth proved case of primary carcinoma of the pancreas in an individual under 20 years of age is reported.

Report of Case

Clinical History: J. S., a boy, 15 years of age, of American parentage, was admitted to the medical service of Cleveland City Hospital, Nov. 4, 1930, complaining of icterus, increasing lassitude and loss of weight. The present illness dated back 5 or 6 months and began with general malaise. During this time he had had numerous attacks of "summer complaint," in which he had had considerable gas and sour, bitter eructations. The jaundice, first noted 3 months prior to admission, had cleared up under a physician's care and frequent doses of castor oil, but had reappeared in 2 to 3 weeks without much change in subjective feeling. Pruritis had been mild. Fatty and sweet foods had been excluded from his diet. He had noticed a few light-colored stools, and the urine had been unusually dark. The patient had lost 15 or 20 pounds in the last 3 months.

Physical Examination: The patient was well developed, well nourished, intelligent and coöperative. The skin and sclerae were markedly icteric; the tonsils were subacutely inflamed. Heart and lungs presented no abnormality. The

liver was slightly tender and enlarged. Other than a phimosis no additional abnormal physical finding was noted.

Laboratory Studies: A persistent uribilinuria and an icteric index ranging from 38 to 60 was revealed. The red blood count was 4,810,000 and the hemoglobin was 92 per cent Sahli. The white blood count fluctuated between 14,000 and 22,000. Differential count revealed an eosinophilia which varied from 21 to 7 per cent. The red blood cells showed an increased fragility to hypotonic saline solutions. The clotting time was 15 minutes by Sabarze's method, as contrasted to 3 to 4 minutes as normal for that method. The bleeding time was 5½ to 6 minutes, the normal being 1 to 3 minutes. The stools contained no bile pigment and no parasites or ova. The blood sugar was 86 mg. per 100 cc.

The temperature fluctuated between 37° and 39° C. The respirations varied between 15 and 24 per minute, the pulse betwen 58 and 120 beats per minute.

Course of Illness: On entry a diagnosis of acute catarrhal jaundice was made but the lack of improvement and persistent eosinophilia suggested intestinal parasitism with obstruction of the common bile duct. An exploratory laparatomy was advised but refused by the parents. The patient was discharged on release, Dec. 27, 1930.

He felt a trifle better and was up and about for 4 weeks until he experienced pain in the region of the liver. This increased in intensity and a severe colicky pain developed in the right upper quadrant with radiation to the back. After 2 weeks in bed he was up and about again but had tenderness and cramps in the upper abdomen. He lost weight progressively and his general condition became worse. The icterus deepened. The patient gradually became weaker and more lethargic until he lapsed into semicoma and was admitted on the surgical service of St. Vincent's Charity Hospital on March 23, 1931.

On admission physical examination revealed marked emaciation, icterus and a tender enlarged liver. No masses were palpable in the abdomen. The patient was semicomatose and apparently moribund. That night, intractable hemorrhage from the left nostril developed and, despite all treatment, persisted until the patient died, 14 hours after admission.

Autopsy Report

Autopsy was performed 2 hours after death. The abdominal cavity contained about 100 cc. of dark, amber-colored fluid. The liver was markedly enlarged. A hard, irregular, rounded nodular mass about 7 cm. in diameter was present in the head of the pancreas and presented a mottled red, blue and yellowish white color. On section the mass showed a variegated, coarsely trabeculated cut surface. The tumor was granular, yellow to yellowish white in color, with irregular hemorrhagic discolorations of brownish red. About the periphery were numerous, enlarged firm lymph nodes, which on section showed the same yellow and white, granular, highly cellular cut surfaces. The rest of the pancreas was definitely atrophic, firm in consistence, with marked increase of interlobar connective tissue stroma. The pancreatic duct was moderately dilated.

The gall-bladder was greatly distended, as was the entire biliary tract. No bile could be expressed into the duodenum except after cutting through the tumor mass and freeing the common bile duct. On opening the duct system the dilatation was found to start 1 cm. from the ampulla of Vater and to extend into the intrahepatic ducts. The biliary obstruction was caused by compression of the common bile duct by the tumor mass, which did not extend into the wall of the duct or the duodenum. The liver weighed 3800 gm. and was diffusely and symmetrically enlarged. Numerous, rounded, yellowish white nodules characterized the capsular and cut surfaces, and the intervening hepatic tissue was a mottled green and brown color. The lobules were abnormally prominent and the perilobular stroma was increased in amount. No metastases other than to the liver and neighboring lymph nodes were found.

Microscopic Examination

Microscopic sections through the pancreatic tumor exhibit irregular masses and interlacing cords of cells with a slight tendency to form acini. These are circumscribed by dense, hyalinized connective tissue. Areas of necrosis and extensive hemorrhage are prominent. Instances of tumor invasion of veins are numerous. The cells vary considerably in size and in form, from cylindrical to spindle shape. The cytoplasm is acidophilic. The nuclei are large, vesicular and situated in the lower portion of the cylindrical cells. Nucleoli are prominent. Numerous normal and a few abnormal mitotic figures are seen. Sections through the rest of the pancreas reveal a marked increase in inter- and intralobular connective tissue, atrophy of the acinous parenchyma and remarkable preservation of the islets of Langerhans. The secretory acini show great variation from closely packed, highly cellular, normal appearing to small, irregular, deeply staining, widely separated acini. Some of the latter show a close resemblance to the tumor tissue.

Sections of the liver reveal early obstructive biliary cirrhosis, with increase of stroma, deposition and phagocytosis of bile pigment, dilatation of sinusoids and bile ducts and an apparent increase in number of periportal bile canaliculi. The tumor metastases show cell groups which tend to assume rounded and rosette-like shapes, for the most part without lumens. Some of the periportal lymphatics and veins contain tumor masses.

The rest of the organs show nothing striking, other than hemorrhage into the nasopharynx, tracheobronchial tree and pelvis of the right kidney. There is a marked, acute pulmonary distention.

The immediate cause of death was asphyxia from hemorrhage into the tracheobronchial tree.

Summary

1. The literature on primary carcinoma of the pancreas in individuals under 20 years of age is reviewed critically.

2. Five proved, reported cases of primary carcinoma of the pancreas in subjects under 20 years of age were found.

3. A sixth case, that of an adenocarcinoma of the pancreas in a 15 year old boy, is reported. The symptomatology and course of the disease were typical of carcinoma of the head of the pancreas with biliary obstruction. Death was due to asphyxia from hemorrhage into the tracheobronchial tree.

4. Two other references to primary carcinoma of the pancreas in children were found. One was unobtainable and the other merely cited a case without giving details.

5. Five other case reports of primary carcinoma of the pancreas in children were found, analyzed and listed as doubtful cases.

Note: I am indebted to Dr. H. T. Karsner for many helpful suggestions and criticisms, and to Dr. Paul Gross, pathologist at St. Vincent's Charity Hospital, for aid in the preparation of this paper.

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BASOPHILIC DEGENERATION OF HEART MUSCLE *

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In 1910, Hewitt,[1] as a result of a study in the Department of Pathology of the University of Minnesota, published a paper entitled, "A Peculiar Degeneration Found in Heart Muscle Cells." Therein he described the lesion as "a small, round, oval, or irregular pale blue area inside of a single muscle cell." He continued, "With high power these degenerations show a slight bluish mottling, somewhat irregularly defined. . . . They sometimes occupy only a portion of the cell, at other times almost the whole of the cell is filled with blue staining material, but always enough of the cell remains to show that it is a heart-muscle cell." As far as the literature has been reviewed, there is no other reference to this type of lesion.

My investigation is based on a study of routinely obtained sections of the heart derived from 320 consecutive postmortem examinations. Blocks of tissue were taken from the septum and both ventricles of each heart that was studied; these were hardened in Orth's fixative and embedded in paraffin. The sections were then stained in the routine manner with hematoxylin and eosin, and in addition with various other stains which will be discussed later.

The lesion described by Hewitt was found in 107, or 33.43 per cent of the 320 hearts examined. The areas of degeneration were of microscopic size. It is my impression that the degeneration passes through several phases. With the hematoxylin and eosin stain, the degenerated portions were seen as basophilic patches which generally occupied the centers of the muscle bundles and frequently included the well preserved, often hypertrophied, nucleus. They always were of well defined limits and at the periphery of each was a zone of normal muscle tissue. No tissue reaction could be seen in the degenerated areas. In the immediate neighborhood, and even in the continuation of the involved muscle bundle, the normal structure was preserved. No gross change in the heart muscle could be observed.

In the early stage of the process these degenerated areas stained a rather dark blue, were fairly dense, finely granular, occasionally

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clumped, and sometimes included fragments of muscle fibers (Fig. 1). As the process advanced these areas stained a lighter blue and what was apparently vacuolization appeared (Figs. 2 and 3). In very advanced stages there was left only a fine network of basophilic, intertwining fibers, which included small tissue spaces (Figs. 4 and 5). In this stage the lesion was rather indistinct. If the lesion were very small, or if the heart muscle were cut transversely, the areas were difficult to find; otherwise they were easily distinguished. They might be scattered diffusely throughout the tissue and only a few could be found, and at other times they might be numerous.

The most frequent single site of the lesion (Table I) was the septum. Closely following this in frequency was the left ventricle; the right ventricle showed fewer lesions. Of the cases in which the lesion was found in more than one site, those in which the septum and left ventricle were involved were the most numerous. It is interesting to note that the lesion was found only five times in the right ventricle alone, and was found in combination in the right ventricle and septum only twice.

There was no significant difference in incidence as to sex. Of the 320 hearts, 204 were from males and 116 from females. The regions of degeneration were found in 70 hearts of males and in 37 hearts of females, or in a total of 107 of the entire 320 hearts.

Considering the incidence of the lesion, it is astonishing that only the preliminary report by Hewitt has been found in the entire literature, as far as it has been reviewed. Hewitt presented 2 cases of basophilic degeneration of the heart muscle which he had found in routine examination of sections of heart. The number of hearts he examined is not given, but his study covered 6 months. In my series of cases basophilic degeneration was found in about a third of the hearts examined routinely.

Hewitt stated that this peculiar degeneration occurred where there was marked proliferation of connective tissue and where there was evidence of pressure atrophy. In hearts I examined it occurred also where there was no proliferation of connective tissue, and the cells appeared slightly hypertrophied. Occurrence of the degeneration in areas of fibrous degeneration within myocardial scars was rather infrequent. In infarcted hearts basophilic degeneration was not seen in the muscular remnants within the fibrous tissue but was frequently found some distance away.

In order to ascertain the nature of the lesion several differentiating stains were used. With fat stain (scharlach R) the areas showed evidence of affinity for the basic component of the stain and appeared a darker grayish blue than the surrounding tissue. In sections stained for iron noticeable changes in the involved areas were not revealed. With Van Gieson's stain there were no special differentiating characteristics. With the Mallory-Heidenhain method the areas of degeneration showed some affinity for aniline blue, but stained a much lighter blue than the connective tissue. With the Mayer carmine method the areas stained distinctly light red, indicating the

TABLE I

Situation of Lesion

Location	Cases
Septum only	32
Left ventricle only	27
Right ventricle only	5
Septum and left ventricle	33
Septum and right ventricle	2
Septum and right and left ventricles	6
Left ventricle and right ventricle	8
Total	113

presence of some kind of mucin or of a substance related to mucin. Hewitt, however, stated that these areas did not take any characteristic stain for mucin. With Best's carmine method the areas of basophilic degeneration stained bright red and were readily distinguished from the bluish gray of the surrounding tissue. It must be kept in mind that the substance in these areas may be related to glycogen, in spite of the fact that the blocks were kept in formalin. It is worth mentioning that a similarity in staining reaction for mucin and glycogen exists in the areas of basophilic degeneration of the heart and in the corpora amylacea of the various organs. The presence of calcium in these areas has been excluded by the acid test. With the Orlandi silver stain the involved areas appeared very pale and gave evidence of some liquefaction. There was no argentophilic reaction to this stain.

To quote Hewitt, who used iodine in the form of compound solution of iodine (Lugol's solution), "these areas, when so stained and

examined under water, appear of a terra cotta pink, somewhat mottled." Although I carried out the procedures exactly as he described them, I could not obtain this reaction with the materials available to me. Hewitt further described, in sections stained with toluidin blue and thionin, "large granulated cells which often are especially abundant about the blood vessels . . . and which are thought to be the same as described by Lustgarten as the parasite of

TABLE II

Anatomical Diagnoses of Cases in which Basophilic Degeneration was found at Postmortem Examination of the Heart

Diagnosis	Hearts examined	Basophilic degeneration found
Malignancy	81	37
Heart disease	52	21
Cholecystitis with cholelithiasis	20	9
Gastro-intestinal ulcers	16	6
Pneumonia	16	9
Peritonitis	15	5
Brain tumor	21	4
Syphilis	9	4
Genito-urinary infection	7	4
Ulcerative colitis	5	2
Empyema of thorax	3	2
Acute pancreatitis	1	1
Electrocution	1	1
Drowning	1	1
Toxemia from burning	1	1

syphilis." This cellular reaction has apparently no local connection with the areas of basophilic degeneration. The presence of these large granulated cells could not be confirmed in any of my specimens, some of which were derived from patients whose condition was diagnosed as syphilis. Of Hewitt's 2 reported cases, 1 was an example of tertiary syphilis, and the other was a case of acute serofibrinous peritonitis with abscesses in the liver and mesentery.

In Table II is shown the frequency of occurrence of basophilic degeneration in my cases, together with the primary pathological diagnosis. The lesion was found most frequently in cases of malignancy and heart disease. It was also found in many cases of infection and inflammation, as well as in a single case each of electrocution, drowning, and toxemia from burns. Because of the multiplicity of condi-

tions with which basophilic degeneration has been found to be associated, it would be difficult to give any one disease entity as the etiological agent.

From Table III it may be seen that the lesion occurs frequently among subjects who have passed the age of 30 years and most frequently among those who are between the ages of 40 and 80 years. Malignancy and a diseased condition of the heart, in association with

TABLE III

Age Incidence

Decade of life	Hearts examined	Basophilic degeneration found	
		Number	Per cent
yrs.			
0–10	27	0	
10–20	8	1	12.50
20–30	17	1	5.88
30–40	40	9	22.50
40–50	43	16	37.20
50–60	70	29	41.42
60–70	73	31	42.46
70–80	39	19	48.70
80–90	3	1	33.33
Total	320	107	33.43

which the lesion was most frequently seen (Table II), generally afflict persons who are 40 to 80 years of age; thus, age seems to be an important, although probably not the only, factor concerned. The factor of toxemia cannot be ignored.

Hewitt quoted Mallory as follows: "The nature of this degeneration is of a hyaline change allied to hydropic degeneration with the presence of some mucin." In an article by Rademaker,[2] which deals with lesions caused by sarcosporidia in the heart muscle, there is a photomicrograph of a stage of the lesion which resembles slightly the picture of the early stage of basophilic degeneration. The change pictured by Rademaker, however, does not correspond in staining reaction to the areas under consideration. No sign or manifestation of parasites could be observed in the great number of sections studied. Because of the strict localization of the lesions, the possibility has to be considered that they are of parasitic origin, but since parasites were not found this possibility does not seem to me to be tenable.

Summary and Conclusions

A peculiar lesion of the heart muscle is described under the term "basophilic degeneration." One subject, in whose heart the lesion was found, had died as early as the 17th year of life, but most of the hearts were from subjects who had died between the ages of 40 and 80 years.

The most frequent sites of the lesion were the septum, the left ventricle, and a combination of the septum and the left ventricle.

Staining reactions showed that the areas contained mucin as well as a component related to glycogen.

It seems probable that toxemia played some part in the etiology of this lesion.

Hematoxylin and eosin was the most valuable stain, because it clearly differentiated the areas of basophilic degeneration.

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DESCRIPTION OF PLATE

Plate 69

Fig. 1. Transverse section. The area of degeneration is fairly large, granular, and stains bluish purple. The nucleus is well preserved. Hematoxylin and eosin. × 700.

Fig. 2. Area of basophilic degeneration in a more advanced stage than is shown in Fig. 1. The periphery of the muscle cell is intact. Hematoxylin and eosin. × 200.

Fig. 3. Higher magnification of a portion of the section shown in Fig. 2. × 550.

Fig. 4. A fairly well advanced stage of basophilic degeneration. Fibers which stained pale blue are seen surrounding remnants of muscle fibers. × 200.

Fig. 5. Higher power of a portion of the section shown in Fig. 4. The area appears distinctly vacuolated. × 550.

1

2

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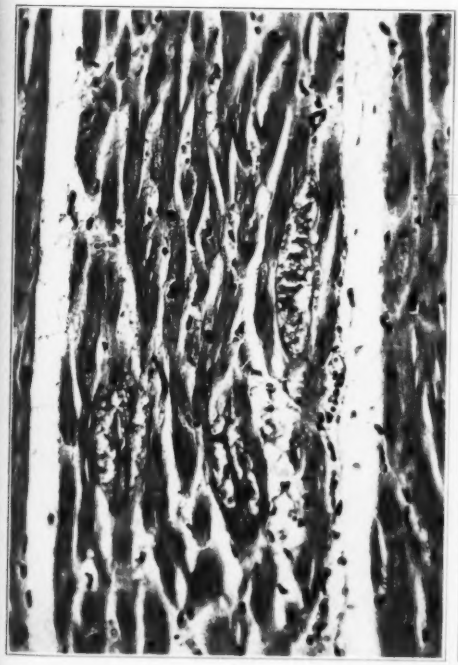

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Haumeder

Basophilic Degeneration of Heart Muscle

ADENO-ACANTHOMA OF THE PYLORUS *

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Adeno-acanthoma of the pylorus is practically unknown and yet carcinoma of the stomach is a very common condition, 60 per cent of all gastric carcinomas originating in the pyloric region (Ewing,[1] and Kaufmann[2]). Thousands of cases have been carefully studied, so that there has been no dearth of material in which to observe the incidence of squamous cell carcinoma in the pylorus. But 3 cases of adeno-acanthoma of the pylorus are recorded in the literature, namely, those of Lubarsch[3] in 1906, Herxheimer[4] in 1907, who first suggested the designation "adeno-acanthoma" for mixed epidermoid and glandular pyloric carcinomas, and Oberling and Wolf[5] in 1927.

Lubarsch[3] reported an adenocarcinoma of the pylorus which had metastasized to the regional lymph nodes. In these metastases he found numerous foci of squamous cell tumor. On reëxamination of the primary tumor in the pylorus he discovered a single area showing typical cornifying prickle cell epithelioma which looked "precisely like cancer of the esophagus."

In Herxheimer's case,[4] at operation a tumor the size of a child's fist was found encircling the pylorus. Miliary nodules studded the serous surface and two enlarged lymph nodes were found behind the pylorus. The remainder of the stomach was tumor-free. The patient died 8 days after operation. At autopsy no metastases or extensions were found and there was no local recurrence.

Histologically the tumor was predominantly an adenocarcinoma. A comparatively small part of the tumor was epidermoid in character. All gradations between adenocarcinoma and prickle cell epithelioma were demonstrable. Pearl body formation was common in the epidermoid areas. Epidermoid masses were especially common in the submucosa and deeper parts of the tumor down to the serosa. The connective tissue between the tumor cell masses contained a moderate number of elastic fibers. Irregular infiltration by round cells was present throughout the tumor.

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The case reported by Oberling and Wolf [5] was that of a female, 67 years of age. Exploratory laparotomy disclosed the parietal peritoneum covered with whitish, often hemorrhagic nodules. The abdominal viscera were adherent and covered with disseminated nodules. At autopsy the neoplastic process was limited to the abdomen. The abdominal viscera were found to be entirely covered with globular masses, reddish to purplish in color and of a gelatinous consistence. A huge, hemorrhagic gelatinous mass weighing 11 Kg. involved the omentum. The stomach was about normal in volume. At the level of the pylorus the gelatinous masses in the serosa were in direct continuity with a homogeneous, whitish infiltration which occupied all layers of the wall and formed an irregular, ulcerated elevation on the mucosa. The liver was seeded with semiliquid viscous nodules up to the size of a man's fist. A nodule of similar appearance was found in the spleen.

Histological examination disclosed a mucous adenocarcinoma of the stomach which in areas presented an intracystic papillary structure lined by clear cells ("analogous with certain renal tumors with clear cells"). In the midst of these glandular elements large cylinders of prickle cell epithelium exhibiting large pearl bodies were found. The authors remarked that the picture was strikingly like cutaneous epithelioma. Adenocarcinoma and epidermoid carcinoma were more or less intermingled, but transition forms between cylindrical and squamous elements were not demonstrable in a study of many sections. The epidermoid formation was confined to the central portion of the glandular tumor. The extragastric tumor was a mucous adenocarcinoma and the metastases were entirely mucoid.

Report of Case

Clinical History: * P. M. entered the hospital, on March 9, 1934. He was a seaman, aged 48 years, and was born in Norway. His father and mother were living and well at the age of 70 years. Three brothers and five sisters were living and well. The patient was the oldest child.

His chief complaint on entering the hospital was pain in the abdomen and vomiting. Prior to Christmas of 1933, his health had been good. At that time his appetite gradually became poor, he was troubled with constipation, belching and epigastric discomfort. About the same time he began vomiting variable amounts of "coffee-ground" material on an average of every 3 or 4 days,

* The clinical and operative summaries were prepared by Drs. Teufel and Van Ackeren of the U. S. Marine Hospital at Seattle, Washington.

and often had black, tarry looking stools. He grew progressively weaker and lost about 20 pounds in weight up to the date of admission. He also became paler than formerly.

Laboratory Data: The blood Wassermann examination was negative, the blood count was 3,300,000 on March 12th, and 3,070,000 on March 21st. The hemoglobin ran 65 to 70 per cent and the stools repeatedly showed occult blood 4 plus. X-ray examination indicated a carcinoma of the pylorus with almost total pyloric obstruction.

Operation: The patient was transfused on March 30th and operated upon on April 2nd. A tumor of the pylorus about 8 cm. in diameter was found. It was not adherent. During the operation, when the stomach was bisected, the large opening gave ample opportunity to examine the proximal end both by inspection and by palpation. There was no evidence of carcinoma. There were no evident metastases in other viscera and enlarged lymph nodes were not found. The tumor was so well confined to the pyloric portion of the stomach that after partial gastrectomy the surgeon felt hopeful of recovery.

After the operation the patient gradually gained weight and strength and the wound healed. Early in May he complained of pain in the operative scar. Palpation suggested a mass in the epigastrium to the right of the scar. On May 12th symptoms of obstruction supervened. The patient was kept under a palliative regimen, but continued to grow worse and died on July 11th.

Surgical Specimen: The formalin-fixed specimen represented the pyloric portion of the stomach and a short segment of the duodenum. The outward appearance was that of a more or less smooth, bulging mass showing fibrous thickening of the covering surface. Dissection of the specimen disclosed two small lymph nodes along the posterior inferior surface. A section through the most prominent portion of the mass revealed an ulcerated, vegetating, more or less cornifying structure protruding into the lumen. The growth gradually tapered off all around into a hard, leathery mucosa, the normal markings of which were ironed out for variable distances before merging with the normally folded and furrowed mucosa. The tumor measured 9 by 6 by 4 cm. The cut surface presented a mosaic of whitish and yellowish, roughly rounded and angular, solid, sharply demarcated masses up to 16 mm. in longest diameter, varying from white to golden yellow in color. These infiltrated through to the serosal surface. Near the distal end of the pylorus they were readily discernible in the submucosa, blended for some distance with the mucosa and stood in sharp contrast to the thick muscularis below, which in this portion appeared intact in gross.

Autopsy Report

The autopsy disclosed massive local extension of the neoplastic process centering from the line of the anastomosis. This mass was adherent to the abdominal wall, the pancreas and the celiac vessels. The omentum was included. The portion of jejunum which had been anastomosed to the stomach was infiltrated for a distance of about 2 inches by a hard leathery growth, which apparently completely encircled it. There were no distant metastases.

Careful dissection of the formalin-fixed specimen disclosed the following. The pars abdominalis of the esophagus, and the cardia of the stomach appeared normal. Below this level the stomach wall showed progressive thickening and more or less suppression of the mucosal plication progressing downward to complete obliteration. In the line of the gastrectomy scar and in the vicinity of the anastomosis the wall reached a thickness of 11 mm. and was so indurated that it cut like cartilage. Here the gastric surface looked and felt like alligator skin, while the sectioned wall presented a ligamentous appearance. The left adrenal gland and a large piece of the body of the pancreas were firmly adherent to the fibrosed gastric serosa. Several medium sized, sclerosed arteries traversed this entangled mass.

Histological Examination

Most of the material studied was impregnated for 48 hours in 2½ per cent potassium bichromate after formalin fixation. In all, thirty-nine blocks were taken from different areas of the surgical specimen and thirty-two from the autopsy material. A number of 43 by 70 mm. paraffin sections were made in order to afford every opportunity for observing transitional and other noteworthy changes. The sections were stained with Weigert's iron chloride hematoxylin and Van Gieson's picro-fuchsin, Mayer's acid hemalum and eosin, a modification of the Romanowsky stain for the demonstration of intercellular bridges, Gram's stain for keratohyaline granules, toluidin blue for mucin, and Weigert's resorcin-fuchsin for elastic fibrils.

The tumor removed at operation is predominantly epidermoid carcinoma. The mass that protruded into the lumen is the counterpart of a cornifying papillary and infiltrating prickle cell epithelioma

of the skin. The normal architecture of the pyloric wall is entirely obliterated by solid, bulky, angular, lobular and elongated masses of squamous epithelium. Keratohyaline granules, cytoplasmic hyalinization, and cornification in all stages are readily demonstrable. Here and there are seen cysts filled with exfoliated squames. The nuclei are large, round and hyperchromatic and show more or less variation in size and density from area to area. Mitoses are numerous. Scattered mono- and multinucleated, squamous, epithelial tumor giant cells are encountered alone, and in epithelial islands, some reaching a diameter of 120μ. Squamous tumor extends through to the serosa. The stroma is scanty, fibroblastic in character and shows small foci of infiltration by lymphocytes. Ramifying elastic fibers are fairly numerous. The intragastric surface shows stretches of ulceration and granulation and heavy deposits of bacteria. It is interesting to note that the epithelium bordering the ulcers is distinctly anaplastic in character and disposed in branching strands which fray out into the stroma.

Most of the sections show only epidermoid carcinoma. A few sections show sporadically disposed solitary glands and small collections of glands lined by medium and tall columnar epithelium with disorderly arranged hyperchromatic nuclei and goblet formation. Within some glands a few swollen signet ring cells are embedded in mucus.

Sections taken near the margins of the bulky mass show increasing numbers of glandular structures, a partly glandular mucosa, and some persistent landmarks of the gastric wall.

In passing from normal to indurated stomach wall there are seen successively glandular hypertrophy, marked vascular engorgement, mucous hypersecretion, accentuation of the stroma, and heavy infiltrations of lymphocytes. Occasionally the glands form mucous cysts. Here and there the lymphoid follicles are greatly enlarged, the submucosa shows a heavy overgrowth of connective tissue and the muscularis also shows ramifying strands of fibrous tissue. The glands become more and more elongated, and apparently normal glands penetrate here and there through the muscularis mucosa and submucosa. Abruptly, the mucosa and penetrating glands present an atypical and hyperchromatic appearance and all layers of the stomach are irregularly infiltrated by orderly and disorderly glands of variable size and shape, lined by medium and high columnar hyper-

chromatic epithelium showing mucus formation and mucous cysts. Scattered intracystic papillary proliferations are found and in these areas the glandular epithelium becomes distinctly of the clear cell type. Copious collections of swollen, mucus-filled signet ring cells are encountered lying loose in the stroma and within glands. Nerves are commonly infiltrated by tumor tissue, occasionally to the point of obliteration. Tumor thrombi are numerous in the submucosal and subserosal vessels. They are invariably of the cylindrical or mucous signet ring cell type. Stretches of hemorrhage and necrosis are encountered throughout the glandular portion of the tumor.

Sections from some indurated areas, in the vicinity of the major tumor mass, show a chronic productive and suppurating process involving the submucosa and muscularis. The mucosal and infiltrating glands appear more anaplastic and the lining epithelium is frequently stratified. Here and there the columnar epithelium becomes cubical and flattened, roughly polygonal cells are seen superimposed upon or interpolated between the cylindrical cells. Elsewhere portions of glands forming mucus show proliferation of pavement epithelium into the lumen, and in some glands the cylindrical epithelium continues insensibly into the peripheral columnar layer of a squamous patch. Plugs of cornifying epithelium are not uncommonly seen in otherwise well formed mucous glands. In some glands the epithelium shows a progressive heaping up of pavement cells, producing tubules lined partly by squamous epithelium and partly by mucus-forming cylindrical epithelium. Here and there stretches of the mucosa show patches of superficially hyperkeratotic, sharply papillary, stratified squamous epithelium grading insensibly into the surrounding adenocarcinomatous mucosa. Other portions of the mucosa show abrupt transitions from adenocarcinoma to epidermoid carcinoma. Sporadic neoplastic glands remain in the stroma of epidermoid areas.

The transitional phases of adenocarcinoma to squamous carcinoma are found in but two sections; however, they are so striking and picturesque as to defy misinterpretation.

The neoplastic process of the gastric mucosa stops abruptly at the junction of pylorus with duodenum, although the submucosa and outer layers of the duodenum are heavily infiltrated by intermingled adenocarcinoma and epidermoid carcinoma.

The two small lymph nodes dissected out from the surgical speci-

men show the sinuses crowded with typical and disorderly mucous glands (adenocarcinoma).

The autopsy material shows that the esophagus and cardia were entirely normal. Below this level, but outside of the area of leathery induration, a low grade chronic productive inflammatory process prevails. This changes abruptly into a diffusely infiltrating adenocarcinoma at the margin where the gastric mucosal pattern becomes obliterated. The indurated mass proper represents a compact, diffusely infiltrating adenocarcinoma showing all the stigmata of a rapidly proliferating carcinoma. The subserosal infiltrations formed mucin in abundance and tumor thrombi in this zone are very common.

While the involved portion of the stomach remaining after partial gastrectomy shows predominantly adenocarcinoma, an occasional focus of epidermoid carcinoma occurs in the line of the old scar, appearing independent of the glandular carcinoma.

The omentum, the lymph nodes and a small piece of pancreas are infiltrated only by adenocarcinoma. The adrenal gland is involved in scar tissue but not by tumor.

Discussion

Squamous cell carcinoma at the gastro-esophageal junction and in the adjacent stomach is not particularly uncommon, but primary squamous cell carcinoma of the cardia is infrequent and difficult to establish as primary there. Squamous cell carcinomas of the stomach usually represent metastases, extensions or implantations from the tongue or from the esophagus. In these cases there is frequently a history of difficulty in swallowing of short duration, rapidly proceeding to esophageal obstruction.

Occasionally the body of the stomach is so extensively involved that the infiltration of the cardiac orifice entirely escapes notice and there is every appearance of a tumor arising in the stomach rather than in the esophagus or at the gastro-esophageal junction. Kaufmann's case, recorded by Herxheimer,[4] presented a large cancerous growth of the posterior wall of the stomach, composed of cornifying squamous epithelium that extended to the esophageal junction. In this case a traumatic ulcer of the cardia was epithelialized from the esophagus and gave rise to the neoplasm. The tumor in Boyden's [6]

case was apparently in the stomach rather than in the esophagus, but it was so high up in the stomach that it completely surrounded the cardiac orifice and in one or two areas had grown along beneath the submucosa beyond the sphincter, so that there was a small amount of tumor actually above the cardia. The gross appearance suggested stomach but the histology was more in favor of esophageal origin. The case reported by Vinson and Broders [7] falls into the above category.

At this point attention is invited to a finding which was reported by Prof. C. Toldt [8] as long ago as 1880, and which has apparently been overlooked by present-day writers, although it is mentioned by von Kölliker.[9] In some children between the ages of 1 and 4 years he found islands of stratified pavement epithelium between the cardiac glands of the stomach beyond the lower end of the esophagus. This has been rediscovered any number of times and new interpretations attached to it. Weidman [10] reported a typical case in a 5 day old infant dying of acute gastritis, under the title of "Heteroplastic Esophageal Mucosa in Stomach." He, too, remarks that these islets of epithelium are not at all uncommon in the stomach. Of course the normal occurrence of islets of stratified squamous epithelium in the gastric cardia can be invoked as a source of squamous cell carcinoma in that location. But no such islets have been observed in the pylorus.

It is indeed coincidental that the case now reported combined all the features noted by Herxheimer,[4] and by Oberling and Wolf,[5] and in addition the major tumor was predominantly an epidermoid carcinoma, whereas in the 3 previously reported cases the epidermoid carcinoma was only a minor portion of the tumor or an accidental finding.

Histogenetic Remarks: Heterotopic squamous epithelium has never been observed in the pylorus. There is no basis for assuming its presence there. The histological picture clearly shows all stages in the transformation of cylindrical epithelium to the squamous type. Herxheimer made the same observation in the tumor reported by him. He, however, was reluctant to ascribe this change to metaplasia alone. He assumes that the change of the cell type does not take place until neoplastic cell growth begins, and then only in cells that are embryologically predisposed thereto.

Various hypotheses have been advanced to explain metaplasia

in such tumors. It would be only speculation to assume a presumptive cause in this case, whether it be inflammatory, regenerative or neoplastic.

NOTE: I wish to express my indebtedness to Drs. W. C. Teufel, G. C. Lake and J. F. Van Ackeren of the United States Public Health Service for the privilege of studying and reporting this case, and to Major V. H. Cornell, Curator of the Army Medical Museum, for the photographs.

SUMMARY

A case of cornifying epidermoid carcinoma occurring with an adenocarcinoma of the pylorus in which definite transitions from glandular to epidermoid carcinoma were present is reported.

The tumor removed at operation was predominantly epidermoid in character, confined to the pylorus and no metastases or other tumor foci were demonstrable.

At autopsy the esophagus and cardia were normal, the tumor in the vicinity of the gastric resection was predominantly adenocarcinomatous and the omentum, lymph nodes and pancreas were infiltrated only by adenocarcinoma.

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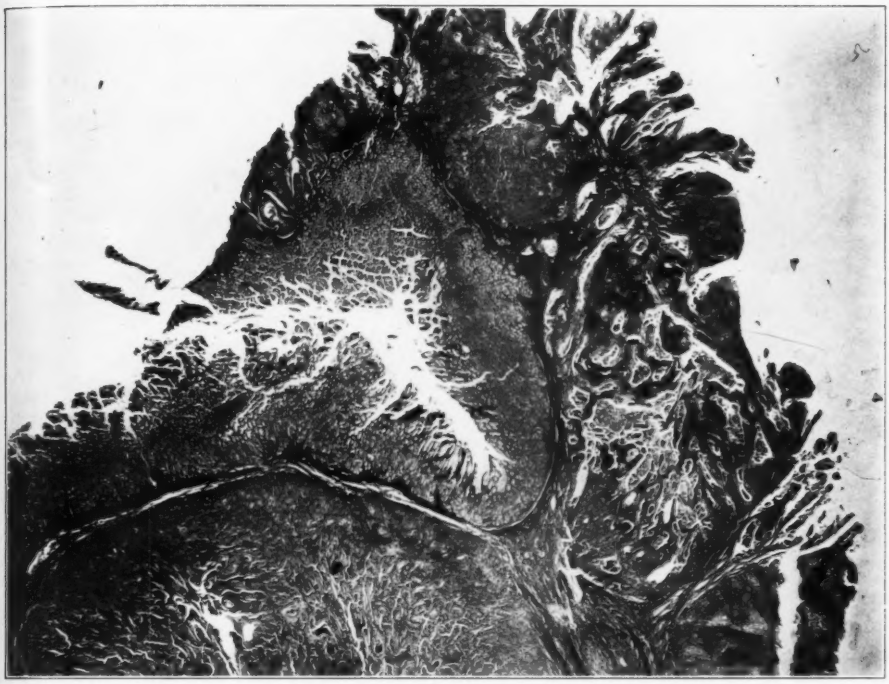
DESCRIPTION OF PLATES

Plate 70

Fig. 1. Thickened fold of pyloric mucosa showing abrupt change to epidermoid carcinoma. (Army Medical Museum Acc. 44510.) × 10.

Fig. 2. Transition of glandular to squamous cell carcinoma. (Army Medical Museum Acc. 44510.) × 200.



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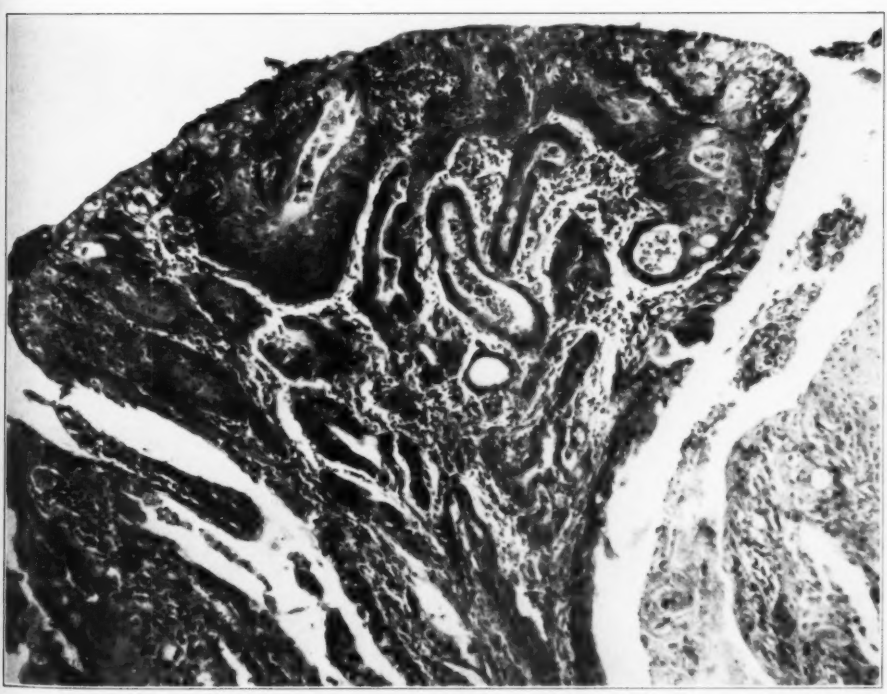

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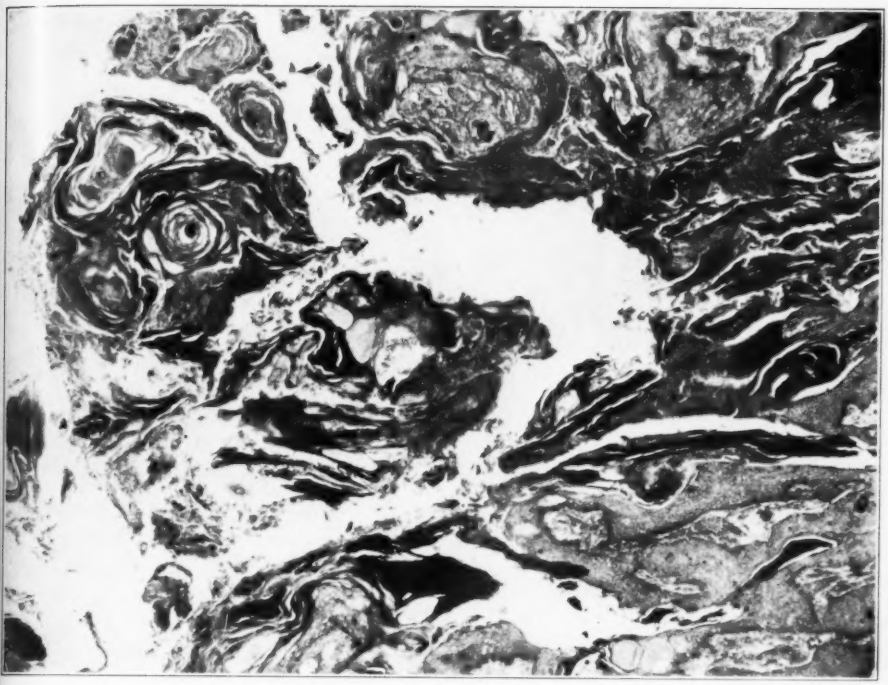
Pasternack Adeno-Acanthoma of the Pylorus

PLATE 71

FIG. 3. Cornifying surface of epidermoid carcinoma projecting into the lumen of the pylorus. (Army Medical Museum Acc. 44510.) × 60.

FIG. 4. Pearl body formation. (Army Medical Museum Acc. 44510.) × 60.



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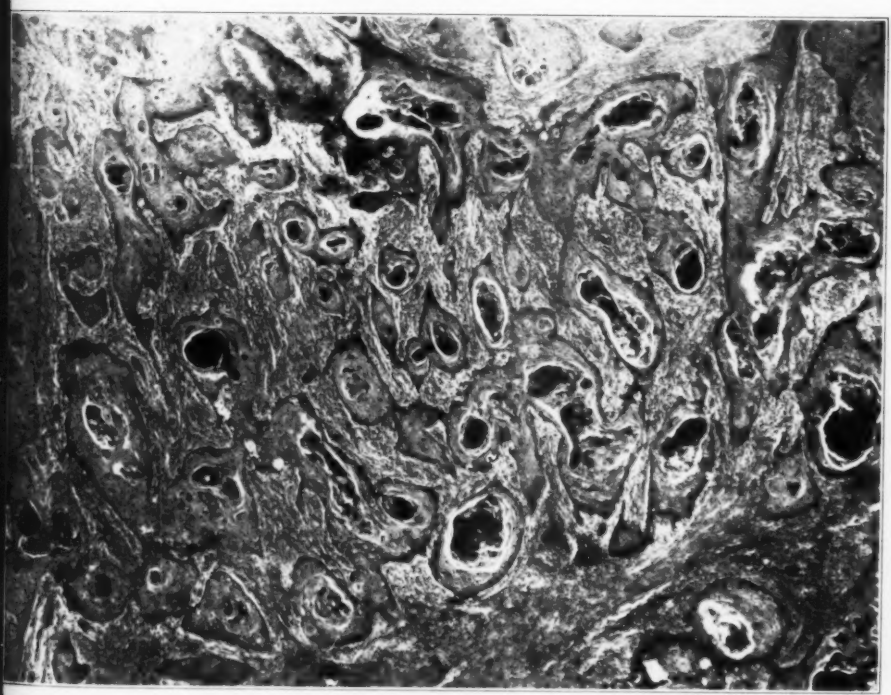

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Pasternack Adeno-Acanthoma of the Pylorus

ERYTHROBLASTOSIS *

REPORT OF A CASE PRESENTING AN ERYTHROBLASTIC TUMOR IN THE THORACIC CAVITY

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Erythroblastosis is a condition in which an early fetal type of blood formation is maintained until term. The disease is characterized by a marked and progressive anemia, a blood picture showing great increase in nucleated red cells, a tendency to bleed from various mucous surfaces or organs, and not infrequently by fetal hydrops or icterus gravis neonatorum. Kleinschmidt [1] believes the stage of hematopoiesis in these infants corresponds to that of the fetus of 3 to 5 months. That this name is descriptive only of one of a group of closely related conditions is obvious from a review of the literature. When both the erythroblastic and myeloblastic series are represented in the blood smears and histological preparations of the tissues it has been called erythroleukoblastosis, and when only the granulocytic series is present the term fetal leukemia has been used. There is more than conjecture to indicate that these conditions are different manifestations of an identical disease of the fetus.

In numerous instances these conditions have been found in association with two other pathological conditions of the fetus, congenital hydrops and icterus gravis neonatorum. Erythroblastosis has been seen without icterus gravis or hydrops but I have not been able to find a report of a case of congenital hydrops or icterus gravis without erythroblastosis, except those in which the examination of the fetus was not sufficiently complete to rule out its presence. One is led to assume that congenital hydrops and icterus gravis are conditions that frequently develop as a result of the blood dyscrasias known as erythroblastosis, erythroleukoblastosis and fetal leukemia.

As an example of this association I refer to a recent article by Ferguson [2] reporting 6 cases of erythroblastosis, all of which were care-

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fully studied. Three of the 6 showed icterus, 2 marked generalized edema, and 1 neither jaundice nor edema.

The clinical features of the disease are as follows. The fetus dies shortly before birth, during birth, or the newborn infant lives but a short time; icterus, generalized edema, and bleeding from some mucous membrane, into the spinal cord, into the meninges, or from the kidneys have been most often observed; those that have hydrops are usually born dead or survive but a very short time. Anemia is marked and progressive; the nucleated cells may exceed 100,000 per cmm., the majority of them being immature erythroblasts or leukoblasts (Wanstrom's case showed 123,700, of which 49 per cent were nucleated red cells). If the infant survives for a time it is likely to have repeated abrupt attacks of cyanosis, in the last of which it dies.

The gross findings at autopsy may be listed as follows. There may be jaundice, congenital hydrops or marked anemia, enlargement of the liver and spleen, hypertrophy of the heart, and hemorrhages, particularly into the meninges. White nodules have been noted in the kidney and Plaut and Bullard [3] observed abnormal smallness of the thymus. The placenta and cord show marked enlargement and increase in weight. Those having congenital hydrops show, in addition to the above, generalized edema, fluid in all the cavities, particularly ascites, and omental "cysts." The cases of icterus gravis have bile-staining of the brain and are likely to be covered at birth by a golden yellow vernix caseosa.

Histologically there is extensive embryonic hematopoiesis in the liver, spleen, pancreas, thymus, lymph nodes, adrenals, kidney, thyroid, and so on. No organ or tissue in which mesodermal tissues exist seems to be exempt. The bone marrow always shows active hematopoiesis. "Bile casts" in the liver are frequently mentioned by Ferguson [2] as typical findings and lipoidosis of the reticulo-endothelial cells of the liver is noted by Wanstrom.[4]

Discussion of the etiology of this group of apparently related conditions is out of place in this paper and at best could only restate a number of hypotheses. It may be permissible, however, to call attention to certain physiological facts concerning the fetus and to certain analogies with adult conditions.

A polycythemia in the newborn is practically a constant normal finding and is presumed to be a response to an oxygen-poor condition in fetal life. Goldbloom and Gottlieb [5] have shown that every new-

born infant has in its blood a large number of immature red cells, either nucleated or reticulated. A reduction in number of red blood cells takes place rapidly the first 24 hours after birth and is down to normal at about 1 week. Coincident with this the immature red cells disappear from the blood stream. During the time they are disappearing an increase in bilirubin takes place in the plasma, leading to visible or concealed jaundice — icterus neonatorum.

These authors show further that if the blood cells of the newborn infant are kept in a test tube, either in contact with the infant's plasma or with physiological sodium chloride solution, an analogous hemolysis takes place and the cells which vanish are, likewise, the immature forms.

There is then, apparently, a fetal mechanism designed for a definite physiological purpose, which bears certain resemblances to erythroblastosis and which, if exaggerated or maintained until term, may become an erythroblastosis.

Extramedullary resumption of blood formation has been seen to occur in several conditions. In a number of instances [6, 7] blood-forming tumors in adult life have been described, usually located in the retroperitoneal tissues.

In 1933 Jaffé [8] pointed out the probable relation of polycythemia vera to the leukemias. One must assume from his work that the excessive production of red cells in erythremia is analogous to that of the white cells in leukemia, especially of the myelocytic type. Furthermore, he offers proof that all cases of leukemia show unusual erythropoiesis in the bone marrow.

We have, of course, seen the so-called leukemic infiltrations in various organs in the course of this disease and accept the present interpretation that these "infiltrations" are areas in which blood formation from primitive mesenchymal tissue, analogous to that seen in the fetus, has been resumed.

It seems to me that the analogy between erythremia and leukemia in the adult and the erythroblastosis and leukoblastosis in the fetus is highly suggestive that the fetal conditions indicated by the various terms erythroblastosis, erythroleukoblastosis and fetal leukemia are identical and are fetal expressions of erythremia and leukemia. Possibly the terms fetal leukemia and fetal erythremia should be used and we should qualify the suitable term with such phrases as, "with hydrops fetalis," "with icterus gravis neonatorum," and so on.

The following report is of an unusual case in that in addition to the evident erythroblastosis there was a blood-forming tumor present in the left thoracic cavity of a newborn infant. I have not found such a condition reported.

Report of Case

Clinical History: Baby boy V., hospital No. 8357, Bryan Memorial Hospital. This baby was the third child of healthy parents. The first two children are living and well. They had no unusual jaundice or edema at birth. The mother had no signs of toxemia and was delivered normally at full term. The only abnormality noted during delivery was an unusually large placenta and cord. These were not weighed.

When about 12 hours old the infant began to have attacks of dyspnea, each of which subsided in a short time. At 32 hours he suddenly became deeply cyanotic. The cyanosis soon disappeared and was replaced by marked pallor. The infant was brought to the hospital when 36 hours old on March 12, 1933.

Examination upon admission showed weight 7 pounds and temperature 101° F. The left half of the chest was smaller than the right, was dull on percussion and no breath sounds were audible over it. The baby held its legs flexed on the thighs and thighs flexed on the abdomen. He had continuous priapism. There was a little oozing of blood from the cord, which stopped on retying. A provisional diagnosis of pulmonary atelectasis was made.

The baby was placed in a Drinker respirator for 12 hours and seemed to improve. When taken out, high pitched breath sounds could be heard over the left lung, the temperature was normal and his color good.

The hips were X-rayed and found to be normal, though the unusual position of the lower extremities persisted and it was very difficult to pull the legs and thighs down to normal posture. Evidently spasticity was present. The priapism was not constantly present after the first few days in the hospital.

No blood examination was made but the urine was examined and found normal. No bleeding from any mucous membrane was observed.

On the fifth hospital day he developed edema of the extremities and face and again showed marked cyanosis. The edema lasted for about 2 days, during which he gained from 4 to 6 ounces per day. The edema and cyanosis then rapidly disappeared and on the 17th day he was taken home apparently in good condition.

The day after dismissal the baby again became blue, the abdomen greatly distended and the rectal temperature rose to 104° F. He was readmitted and placed in the respirator. There was increasing cyanosis and he died at 6 P.M. on the day of the second admission.

Abstract of Autopsy Protocol

The most striking abnormality was a tumor 4.5 by 6 cm. in diameter and 2 cm. thick, firmly attached to the posterior wall of the left pleural cavity and intimately connected with the hilum of the lung, so that the left main bronchial stem and the pulmonary artery

passed through a small portion of the tumor. In removing this tumor from the chest wall it was torn and several cc. of a semifluid material somewhat resembling pus escaped.

On examination the tumor (Fig. 6) had an irregular disc shape and was covered on the visceral surface by a smooth thin membrane resembling pleura. The color of this surface was reddish blue, resembling that of spleen. The surface attached to the chest wall and that portion connected with the hilum were torn, irregular and ragged. There was a central necrotic area from which the pus-like material had escaped. The tissue surrounding this cavity and composing the greater part of the mass was of unusual consistence and mottled in color from gray through the reds to brown.

The left lung was considerably smaller than the right and composed of two lobes. The lung was air-containing throughout but dark red and moist on the cut surface. There were a number of small, subpleural hemorrhages.

The organs were not weighed. The spleen and liver were recorded as about normal in size. The liver was rather meaty and deep red. The spleen was dark red on the cut surface.

Other significant abnormalities noted were a rather marked edema of the omentum so that it seemed distended with fluid, and an enlargement of the testicles, apparently due to edema.

An examination of the central nervous system was not permitted. The spasticity of the legs and the priapism suggested a lesion of the cord or of the cerebrum, perhaps hemorrhage or infiltration, and it is to be regretted that we could not examine them at autopsy.

Histological Examination

The material studied consisted of sections of heart, lung, spleen, liver, suprarenal gland, kidney and the thoracic tumor. Sections of these tissues were stained with hematoxylin and eosin. In addition, sections of the tumor were stained with Wright's stain, Castroviejo's modification of Van Gieson's stain, Bielschowsky, hematoxylin and eosin-azur II, and the azocarmine modification of Mallory's collagen stain. The unusual findings are limited to the liver, suprarenal gland, spleen and the tumor.

Liver: The normal liver structures are well formed and well preserved. Scattered throughout the section, but somewhat more pro-

fusely near the capsule, are irregular islands of foreign cells. These cells are in groups, having from a very few to many cells per group. A nest of cells may lie isolated or many groups may be seen in a limited area (Fig. 1). They lie in the sinusoids, which are distended by them.

The cells themselves (Fig. 3) are much smaller than the liver cells, roughly spherical, though when crowded they may be somewhat fusiform. The nuclei are hyperchromatic with a distinct nuclear membrane. They usually show a single nucleolus. The chromatin is scattered in masses and thread-like pieces. The cytoplasm is relatively narrow, has a faintly granular appearance and is somewhat basophilic. When these cells are crowded together closely they give the impression of being a syncytial mass but, at the periphery, cell outlines can be distinguished.

While the type of cell just described predominates, one can find all stages of erythroblast formation. One may observe gradual assumption of hemoglobin with resulting polychromatophilia, gradual shrinking and condensation of the nucleus, mitotic figures, and finally mature erythrocytes.

Much less easily found in the liver are the various stages of granulocyte development, but it is possible to identify myeloblasts and various types of myelocytes. No megakaryocytes are seen.

It seems certain that the islands of young cells are hematopoietic in character and essentially erythropoietic. The young cells correspond in every way to those described and illustrated by Maximow [9] as proerythroblasts and by Jaffé [8] as erythrogonia.

Suprarenal Gland: In the suprarenal gland, in the inner border of the zona reticularis, a few similar hematopoietic foci are found (Fig. 2).

Spleen: Erythroblastic activity is present in the spleen and the whole series from the proerythroblast to the erythrocyte can be traced. There is not, however, such distinct formation of hematopoietic islands as seen in the liver and suprarenal gland, and it seems that here the process is less evident than in any of the other organs described.

Tumor: The tumor is surrounded by a capsule of loose connective tissue and covered on the free surface by a mesoendothelium. From the capsule numerous septa of loose connective tissue project into the mass at approximately right angles. These septa split and re-

unite in such a way as to divide the tumor into numerous alveolus-like spaces. These spaces vary greatly in size and are filled with cells (Fig. 4), the character of which will be described and illustrated below. There is no reticulum within the alveolus-like spaces and the few definite blood vessels present are in the septa and capsule.

Attention is first directed to the septa. They are composed of loose connective tissue, the ground work of which is homogeneous, contains but few fibrils and in many instances none. In this ground substance are seen nuclei varying from elongated, bluntly fusiform to roughly spherical in shape. These nuclei are rather vesicular and have a sparse, loosely arranged chromatin network.

At the ends of these septa, along their margins and within them, certain changes are seen to take place, these changes being identical wherever they occur. They are more easily traced when they occur within the septum and are as follows. The nuclei, described above as elongated and bluntly fusiform with loose chromatin arrangement, become rounded and the chromatin more dense. Whenever this happens there is an accumulation of several nuclei, the ground substance liquefies and a space is formed in which the cells containing these nuclei are seen to lie (Fig. 5). At this stage these nuclei resemble those described in the liver as erythrogonia or proerythroblasts (compare Figs. 3 and 5) and are surrounded by a narrow field of basophilic cytoplasm like those in the liver. The space in which they lie is not lined by endothelium.

As a result of these changes the margins of the septa are lined with, and the spaces within them are filled with, cells similar to the proerythroblasts of the liver and they develop from the cells of the primitive mesenchyme-like tissue of the septa. As one leaves the septa and examines the cells within the alveolus-like space between them all stages of development of the erythrocyte are seen. The mature red cells are as a rule most numerous near the central part of the alveolus.

Myeloblasts, myelocytes and mature granulocytes are less numerous than in the liver, though occasionally a small area can be found in which they are present. One cell closely resembling a megakaryocyte was found.

It is my belief that the process described in the liver, in the spleen, in the suprarenal gland and in the tumor is almost pure erythroblastic activity, and that the tumor is an erythroblastoma.

Unfortunately, bone marrow, pancreas, thymus and central nervous system were not represented among the tissues preserved at autopsy.

Summary

A brief review of the pertinent literature is given, with special reference to the relation between erythroblastosis, erythroleukoblastosis and fetal leukemia.

Attention is drawn to the fetal mechanism apparently designed to meet oxygen-poor conditions of intrauterine life, an erythremia with a large number of immature red blood cells, and to their rapid reduction in number immediately following birth.

The possible analogy is pointed out between erythroblastosis and fetal leukemia on the one hand, and adult polycythemia vera and leukemia on the other.

The probable rôle of fetal hydrops and icterus gravis neonatorum as complications of erythroblastosis and fetal leukemia is stressed.

Finally, a case of erythroblastosis in a newborn infant having an erythroblastoma in the left pleural cavity is reported with autopsy findings and description of the histopathology.

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DESCRIPTION OF PLATE

PLATE 72

FIG. 1. Liver. Islands of embryonic blood cells lying in the sinusoids of the liver are seen as dark masses of varying size and irregular distribution.

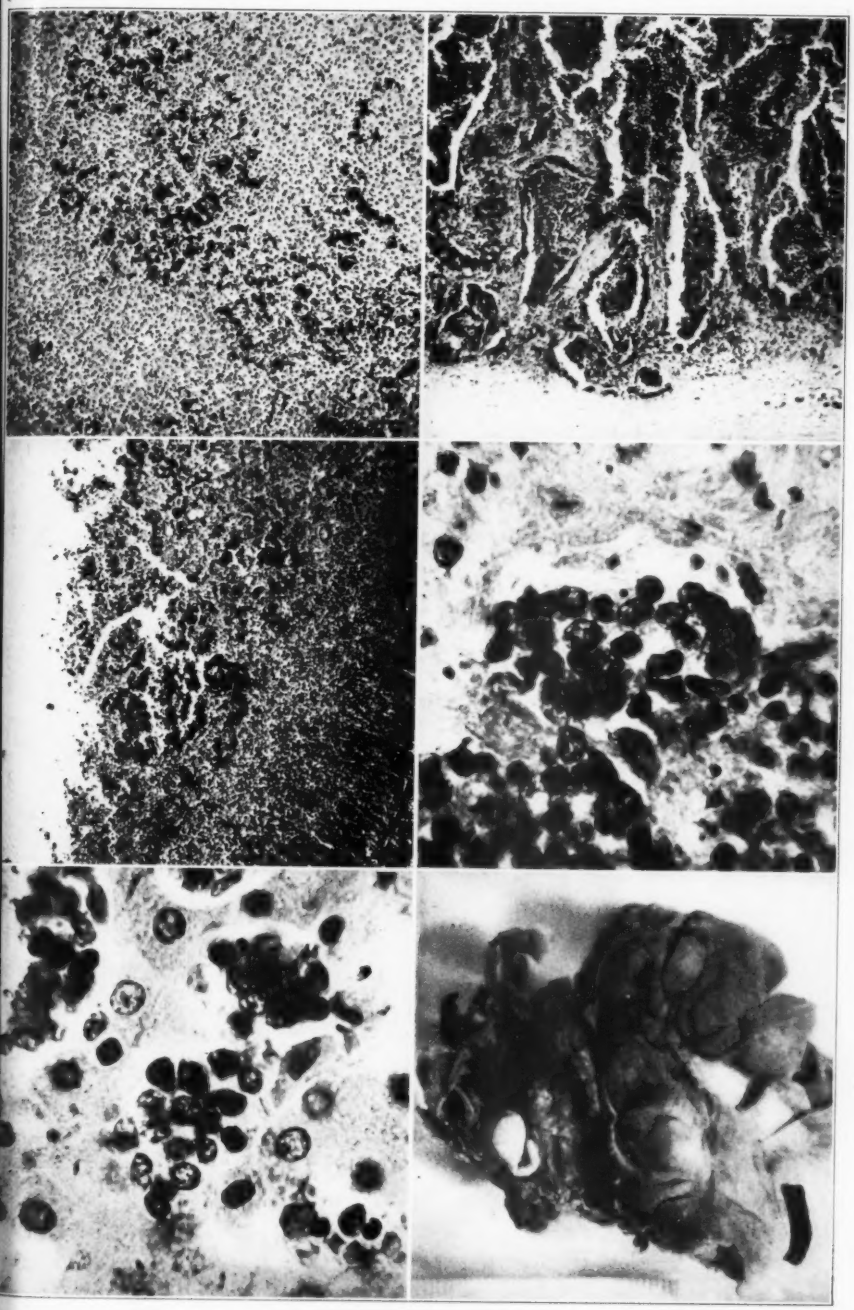
FIG. 2. Suprarenal gland. Islands of embryonic blood cells are seen in the zona reticularis.

FIG. 3. Liver. One of the collections of embryonic blood cells occupies the central portion of the illustration. Most of these cells are proerythroblasts, although several normoblasts are present.

FIG. 4. Thoracic tumor. Note the septa dividing the tumor into irregular, alveolus-like spaces which are filled with cells.

FIG. 5. Thoracic tumor. A nest of proerythroblasts in a space within one of the septa. Note the likeness to the cells in Fig. 3. A few normoblasts and intermediate forms may be seen here also.

FIG. 6. Thoracic tumor. The irregular margin at the left is the portion which was attached to the hilum structures of the left lung.



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5

6

Covey

Erythroblastosis

ALTERATION IN SERUM BILIRUBIN AND BROMSULPHALEIN RETENTION IN RELATION TO MORPHOLOGICAL CHANGES IN THE LIVER AND BILE PASSAGES IN CATS WITH TOTAL BILIARY STASIS *

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Experimental obstruction of the common bile duct has been employed by a number of investigators for the purpose of studying various problems of hepatic and biliary tract function and the pathogenesis and pathological basis of obstructive jaundice. There have been comparatively few attempts, however, to correlate changes in hepatic function with the morphological changes in the liver at varying intervals during total bile stasis in experimental animals.

The present study consists of determinations of the serum bilirubin concentration and degree of bromsulphalein retention in a series of 29 cats with uncomplicated total bile stasis produced by ligation of the common duct. Sections of liver were secured practically simultaneously with the chemical observations in most cases, either at laparotomy or autopsy. Simultaneous morphological and functional data were thus obtained for almost every 24 hour period up to the 16th day following ligation of the common duct. The morphological observations were supplemented by those made on a series of 46 cats previously described by Stewart and Lieber.[1]

The animals employed were adult cats, maintained on a diet of fresh scrap meat and milk. Operation was performed under light ether anesthesia, the abdomen being carefully prepared by clipping, Harrington's solution and alcohol. The common duct was isolated, and in some cases was divided between ligatures, and in others was firmly ligated with $\frac{1}{8}$ inch tape close to the duodenum for the purpose of subsequent release of obstruction. The gall-bladder was left *in situ* in 10 cases, the remainder being subjected to either cholecystectomy (14) or cystic duct ligation (1). In 4 additional cases

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cholecystectomy or cystic duct ligation had been performed several weeks prior to ligation of the common duct. In several instances sections of normal liver were taken for purposes of comparison. In animals in which serial determinations of bilirubin and bromsulphalein retention were made, blood was obtained from the femoral vein. In the others, blood was withdrawn by cardiac puncture. Sections of liver were obtained either at laparotomy or autopsy. All cases that showed evidence of infection (other than a small localized stitch abscess) were excluded, as were several in which spontaneous or traumatic perforation of the common duct had occurred. In no case was there any evidence of reconstruction of the common duct or of passage of bile into the duodenum through anomalous ducts. The animals were killed by incising the heart under light ether anesthesia. A few animals which died spontaneously were discarded if postmortem changes were noted.

Pieces of liver were fixed in 10 per cent formalin. A portion of the fixed tissue was frozen and sectioned and stained for fat; the remainder was blocked in paraffin, cut and stained with hematoxylin and eosin. Serum bilirubin was determined by the method of van den Bergh, as modified by Thannhauser and Andersen.[2] Bromsulphalein was injected intravenously in the dosage of 2 mg. per kilogram of body weight, the degree of retention being estimated in specimens of blood withdrawn 30 minutes after administration of the dye.

Résumé of Lesions Associated with Complete Biliary Stasis in the Bile Ducts of Cats

The bile ducts undergo progressive but irregular dilatation, roughly in proportion to their original size. The walls of the extrahepatic ducts become attenuated and later slightly thickened. White bile may form rather rapidly. Proliferation of the smaller ducts is noted early, while the mucosa of the larger ducts undergoes enormous proliferation, particularly after the 10th day. By the 21st day the majority of the hepatic lobules are surrounded by a collar of proliferating small bile ducts. Destruction of these newly formed ducts may occur either as a result of distention with hyaline material and phagocytic cells or, in the late stages of stasis, as a result of the organization of areas of hyaline necrosis.

Pigmentation: Bile pigmentation is similar to that observed in

other animals but, in general, tends to be less marked and is not always proportional to the duration of stasis or the degree of bilirubinemia.

Regressive Changes: These are present (1) in the inner portion of the lobule, (2) immediately beneath the capsule of the liver, (3) sporadically throughout the hepatic parenchyma and (4) about the larger bile ducts. The necrotic cells in most situations are being constantly replaced by regenerated hepatic cells until the terminal stages of stasis, when the process of regeneration fails. In the subcapsular zone, however, the degenerative changes tend to remain stationary unless complete necrosis supervenes.

Focal Necrosis: Focal midzonal areas of necrosis are occasionally noted at the end of 5 hours, are most numerous between 24 and 48 hours and then decrease steadily, being entirely absent after the 13th day. The material in the areas of necrosis is cleared away and the parenchyma is restored to normal by regeneration of hepatic cells and by the ingrowth of liver cords from the surrounding tissue. Organization occasionally occurs if there has been a preliminary exudation of fibrin in the necrotic area.

Hyaline Necrosis: Within the first 24 hours the hepatic cells sporadically throughout the lobules, but especially immediately beneath the capsule, undergo a hyaline type of necrosis. The necrotic process occurring sporadically throughout the lobules is accompanied by a simultaneously developing regenerative process, as a result of which the necrotic cells are being constantly replaced by newly formed hepatic cells. The subcapsular areas of hyaline necrosis are frequently overlaid by a fibrinohemorrhagic peritoneal exudate. These areas undergo a characteristic type of repair which differs in several essential respects from that mentioned above. After the 5th day, increasing in frequency with prolonged stasis, an acidophilic hyaline type of necrosis appears which involves sporadically groups of 6 to 8 cells and variable portions of single or several lobules in the vicinity of portal radicles. These lesions undergo organization and the newly formed connective tissue, slowly contracting, pinches off and destroys the vascular and biliary channels of the neighboring portal radicles. The simultaneous progression of these processes of necrosis and fibrosis results in an extreme degree of concentric avascular fibrosis. Small collections of bile pigment are frequently seen in or about these fibrotic areas.

Vascular Changes: In the early stages there is usually dilatation of the branches of the hepatic and portal veins and of the lymphatic vessels in the portal radicles. The sinusoids are usually compressed by dilating bile ducts at the periphery of the lobules and may show focal or diffuse hyperemia in other areas. The blood vessels may be partially or completely occluded by hyaline or fibrinous thrombi, which may or may not be associated with focal midzonal areas of necrosis. There is a constant increase in the reticulum and connective tissue about all the vascular structures, particularly in the portal radicles where obliteration eventually occurs as a result of the organization of the hyaline necroses.

Regeneration: Evidences of regeneration are noted within 8 hours. These are characterized by budding and fission of the nuclei, leading to binucleation and multinucleation and to the formation of large hepatic cells with hyperchromatic nuclei. By the end of 48 hours, in the majority of cases, this type of regeneration gives way to the mitotic division of hepatic cells which predominates from this time on, although both processes may contribute to the maintenance of the normal hepatic parenchyma which is subject to repeated injury throughout the entire course of stasis. Regeneration lags after the 15th day, as evidenced by the more frequent occurrence of regressive lesions, which tend to progress, mitotic figures and binuclear cells appearing only occasionally.

Experimental Data

Since practically no difference was noted in the morphological changes in the cholecystectomized and non-cholecystectomized animals, these two groups will not be separated in the presentation of the pathological lesions. In order to avoid unnecessary repetition, the findings characteristic of each day of stasis in the 29 animals included in the present study will be outlined and any unusual observations will be mentioned in the individual protocols.

One Day Stasis: Moderate dilatation of the extrahepatic ducts; absent to moderate dilatation of the medium sized intrahepatic ducts; absent to beginning proliferation of the smaller ducts; no thickening of the medium sized ducts; no proliferation of the mucosa of the bile ducts; subcapsular hyaline necrosis absent to marked; sporadic hyaline necrosis slight to moderate; sporadic nondescript

necrosis slight to marked; focal midzonal necroses absent to numerous; no fibrosis about portal radicles; slight to marked cytoplasmic vacuolization; no mitotic figures; pigmentation slight to moderate; occasional sinusoidal thrombosis.

CAT 130. 6/5/34. Ligation common duct, cholecystectomy. 6/6/34. Serum bilirubin 0.32 mg., bromsulphalein, no retention.

CAT 131. 6/6/34. Ligation common duct, cholecystectomy. 6/7/34. Serum bilirubin 0.68 mg., bromsulphalein, no retention.

CAT 132. 6/7/34. Ligation common and cystic ducts. 6/8/34. Serum bilirubin 2.04 mg., bromsulphalein 20 per cent.

Two Day Stasis: Moderate dilatation of extrahepatic ducts; slight to moderate dilatation medium sized intrahepatic ducts; slight proliferation smaller ducts; absent to slight thickening of medium sized ducts; slight to moderate proliferation of mucosa of ducts; subcapsular hyaline necrosis absent to stage of repair; sporadic hyaline necrosis slight to moderate; sporadic nondescript necrosis slight to marked; focal midzonal necroses frequent; beginning fibrosis about portal radicles; slight cytoplasmic vacuolization; no mitotic figures; slight to marked pigmentation.

CAT 143. 6/27/34. Ligation common duct, gall-bladder *in situ*. 6/29/34. Serum bilirubin 0.74 mg., bromsulphalein 35 per cent. Bile in ducts pale green.

CAT 144. 6/27/34. Ligation common duct, gall-bladder *in situ*. 6/29/34. Serum bilirubin 0.0 mg., bromsulphalein, no retention.

CAT 147. 7/3/34. Ligation common duct, cholecystectomy. 7/5/34. Serum bilirubin 2.4 mg., bromsulphalein 100 per cent.

Three Day Stasis: Moderate to marked dilatation extrahepatic ducts; slight dilatation medium sized intrahepatic ducts; slight proliferation smaller ducts; slight thickening medium sized ducts; slight proliferation duct mucosa; subcapsular hyaline necrosis present; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent; slight fibrosis about portal radicles; moderate cytoplasmic vacuolization; no mitotic figures; pigmentation moderate.

CAT 83. 12/27/33. Ligation cystic duct. 3/12/34. Ligation common duct, cholecystectomy. 3/13/34. Serum bilirubin 0.84 mg., bromsulphalein 20 per cent. 3/14/34. Serum bilirubin 0.80 mg., bromsulphalein 45 per cent. 3/15/34. Serum bilirubin 0.76 mg., bromsulphalein 80 per cent.

CAT 88. 1/4/34. Ligation cystic duct. 3/5/34. Ligation common duct. 3/6/34. Serum bilirubin 0.35 mg., bromsulphalein 40 per cent. 3/7/34. Serum bilirubin 0.92 mg., bromsulphalein 40 per cent. 3/8/34. Serum bilirubin 1.4 mg., bromsulphalein 100 per cent.

Four Day Stasis: Moderate to marked dilatation extrahepatic ducts; moderate dilatation medium sized intrahepatic ducts; moderate thickening medium sized ducts; moderate proliferation duct mucosa; subcapsular hyaline necroses undergoing repair; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent; beginning fibrosis about portal radicles; slight cytoplasmic vacuolization; no mitotic figures; slight pigmentation.

CAT 87. 1/4/34. Ligation cystic duct. 3/5/34. Ligation common duct. 3/6/34. Serum bilirubin 0.61 mg., bromsulphalein 100 per cent. 3/7/34. Serum bilirubin 1.12 mg., bromsulphalein 100 per cent. 3/9/34. Serum bilirubin 2.16 mg., bromsulphalein 100 per cent.

Six Day Stasis: Marked dilatation extrahepatic ducts; moderate to marked dilatation medium sized intrahepatic ducts; moderate to marked proliferation smaller ducts; moderate thickening medium sized ducts; moderate to marked proliferation duct mucosa; late stages of repair of subcapsular hyaline necrosis; sporadic hyaline necrosis slight to marked; sporadic nondescript necrosis slight to marked; focal midzonal necroses absent to slight; slight to moderate fibrosis about portal radicles; moderate cytoplasmic vacuolization; mitotic figures present; pigmentation slight to moderate.

CAT 145. 7/3/34. Ligation common duct, gall-bladder *in situ*. 7/9/34. Serum bilirubin 0.47 mg., bromsulphalein 5 per cent. Wide zone subcapsular degeneration.

CAT 146. 7/3/34. Ligation common duct, gall-bladder *in situ*. 7/9/34. Serum bilirubin 0.47 mg., bromsulphalein 5 per cent. Wide zone subcapsular degeneration and vacuolization.

CAT 63. 2/12/34. Cholecystectomy. 5/8/34. Ligation common duct. 5/14/34. Serum bilirubin 1.91 mg., bromsulphalein 70 per cent.

CAT 154. 7/10/34. Ligation common duct, cholecystectomy. 7/16/34. Serum bilirubin 15.2 mg., bromsulphalein 50 per cent.

Seven Day Stasis: Marked dilatation of extrahepatic ducts; moderate to marked dilatation of medium sized intrahepatic ducts; moderate to marked proliferation of smaller bile ducts; moderate to marked thickening of medium sized ducts; moderate to marked proliferation of duct mucosa; subcapsular hyaline necrosis absent; sporadic hyaline necrosis slight to marked; sporadic nondescript necrosis slight to marked; focal midzonal necroses absent; fibrosis about portal radicles slight to moderate; cytoplasmic vacuolization

moderate to marked; mitotic figures present; pigmentation slight to marked.

CAT 150. 7/3/34. Ligation common duct, gall-bladder *in situ*. 7/10/34. Serum bilirubin 4.5 mg., bromsulphalein 50 per cent. Smaller ducts disappearing on account of accumulation of hyaline material.

CAT 151. 7/3/34. Ligation common duct, gall-bladder *in situ*. 7/10/34. Serum bilirubin 8.5 mg., bromsulphalein 40 per cent.

CAT 114. 5/15/34. Ligation common duct, cholecystectomy. 5/22/34. Serum bilirubin 6.27 mg., bromsulphalein 100 per cent.

Eight Day Stasis: Marked distention of extrahepatic ducts; bile frequently pale green, thin consistence; slight to moderate dilatation medium sized ducts; marked proliferation smaller ducts; moderate to marked thickening medium sized ducts; moderate to marked proliferation duct mucosa; subcapsular hyaline necrosis absent; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent or occasional; moderate fibrosis about portal radicles; cytoplasmic vacuolization slight; mitotic figures present; pigmentation moderate to marked.

CAT 82. 12/27/33. Ligation cystic duct. 3/12/24. Ligation common duct, gall-bladder atrophied and contracted. 3/13/34. Serum bilirubin 1.24 mg., bromsulphalein 30 per cent. 3/14/34. Serum bilirubin 1.72 mg., bromsulphalein 55 per cent. 3/15/34. Serum bilirubin 2.24 mg., bromsulphalein 80 per cent. 3/16/34. Serum bilirubin 3.16 mg., bromsulphalein 80 per cent. 3/19/34. Serum bilirubin 6.5 mg., bromsulphalein 30 per cent. 3/20/34. Serum bilirubin 6.8 mg., bromsulphalein 100 per cent.

CAT 120. 5/24/34. Ligation common duct, cholecystectomy. 6/1/34. Serum bilirubin 2.16 mg., bromsulphalein 50 per cent.

CAT 121. 5/24/34. Ligation common duct, cholecystectomy. 6/1/34. Serum bilirubin 3.18 mg., bromsulphalein 60 per cent. Numerous binucleate and hyperchromatic hepatic cells.

Ten Day Stasis: Marked to enormous dilatation extrahepatic ducts; bile commonly pale green or brown, variable consistence; moderate dilatation medium sized intrahepatic ducts; marked proliferation smaller ducts; moderate thickening medium sized ducts; marked proliferation duct mucosa; subcapsular hyaline necrosis occasionally present; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent; fibrosis about portal radicles slight; cytoplasmic vacuolization slight; mitotic figures absent; pigmentation moderate.

CAT 77. 4/13/34. Ligation common duct, gall-bladder *in situ*. 4/14/34. Serum bilirubin 0.91 mg., bromsulphalein 45 per cent. 4/16/34. Serum bili-

rubin 1.31 mg., bromsulphalein 15 per cent. 4/18/34. Serum bilirubin 1.6 mg., bromsulphalein 40 per cent. 4/23/34. Serum bilirubin 0.96 mg., bromsulphalein 55 per cent.

CAT 155. 7/13/34. Ligation common duct, cholecystectomy. 7/23/24. Serum bilirubin 6.5 mg., bromsulphalein 40 per cent. Marked compression of hepatic parenchyma about larger bile ducts. Areas of hyaline necrosis spreading out from larger portal radicles.

Eleven Day Stasis: Marked distention extrahepatic ducts; bile frequently dark green or brown, variable consistence; medium sized intrahepatic ducts frequently compressed, occasionally dilated; marked proliferation smaller ducts; marked thickening medium sized ducts; slight proliferation duct mucosa; subcapsular hyaline necrosis occasionally present; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent; moderate fibrosis about portal radicles; cytoplasmic vacuolization moderate; no mitotic figures; pigmentation marked.

CAT 64. 4/23/34. Ligation common duct, gall-bladder *in situ*. 5/4/34. Serum bilirubin 1.88 mg., bromsulphalein 20 per cent.

CAT 72. 4/23/34. Ligation common duct, gall-bladder *in situ*. 5/4/34. Serum bilirubin 2.48 mg., bromsulphalein 30 per cent.

CAT 123. 5/24/34. Ligation common duct, cholecystectomy. 6/4/34. Serum bilirubin 4.8 mg., bromsulphalein 85 per cent. Localized sinusoidal congestion.

CAT 122. 5/24/34. Ligation common duct, cholecystectomy. 6/4/34. Serum bilirubin 4 mg., bromsulphalein 75 per cent.

Twelve Day Stasis: Enormous distention extrahepatic ducts; bile frequently dark green; medium sized intrahepatic ducts usually compressed; moderate to marked proliferation smaller bile ducts; marked thickening medium sized ducts; slight proliferation duct mucosa; subcapsular hyaline necrosis occasionally present; sporadic hyaline necrosis moderate; sporadic nondescript necrosis moderate; focal midzonal necroses absent; marked fibrosis about portal radicles, bile ducts and sublobular veins; very slight cytoplasmic vacuolization; no mitotic figures in hepatic cells but some in bile duct epithelium; pigmentation marked.

CAT 116. 5/10/34. Ligation common duct; gall-bladder *in situ*. 5/22/34. Serum bilirubin 2.92 mg., bromsulphalein 100 per cent.

Fifteen Day Stasis: Enormous dilatation extrahepatic ducts; compression of medium sized intrahepatic ducts; marked proliferation smaller ducts; marked thickening medium sized ducts; marked pro-

liferation duct mucosa with stretching and thinning of walls of larger intrahepatic and extrahepatic ducts; subcapsular hyaline necrosis absent; sporadic hyaline necrosis marked; sporadic nondescript necrosis marked; focal midzonal necroses absent; moderate fibrosis about portal radicles with obliteration of vessels and bile ducts; cytoplasmic vacuolization slight; no mitotic figures; pigmentation marked; marked compression and atrophy of parenchyma.

CAT 128. 5/28/34. Ligation common duct, cholecystectomy. 6/12/34. Serum bilirubin 1.44 mg., no bromsulphalein retention. Bile dark green.

Sixteen Day Stasis: Enormous distention extrahepatic ducts, bile at times dark green; compression medium sized intrahepatic ducts; marked proliferation smaller ducts; marked thickening walls medium sized ducts; proliferation larger duct mucosa with stretching and thinning of walls; subcapsular hyaline necrosis absent; sporadic nondescript necrosis marked; focal midzonal necroses absent; marked fibrosis about portal radicles with obliteration of vessels and ducts; cytoplasmic vacuolization slight; no mitotic figures; pigmentation slight to marked; large areas hyaline necrosis about portal radicles; marked compression and atrophy of parenchyma about larger ducts.

CAT 125. 5/26/34. Ligation common duct, cholecystectomy. 6/11/34. Serum bilirubin 3.4 mg., bromsulphalein 100 per cent.

CAT 129. 5/28/34. Ligation common duct, cholecystectomy. 6/13/34. Serum bilirubin 2.62 mg., bromsulphalein 30 per cent.

DISCUSSION

Serum Bilirubin

Bilirubin is not present in the blood of the normal cat in sufficient concentration to be detected by means of the van den Bergh reaction. As is true of the dog, from the standpoint of renal excretion it may be regarded as a non-threshold substance. In the present experiment no attempt was made to measure the urinary elimination of bile pigment, but it was obviously present in the urine in every case at the end of 24 hours of biliary stasis.

Several observers have studied the development of hyperbilirubinemia following common duct ligation. The time of appearance of a definite increase in serum bilirubin has varied from 5 minutes, as reported by Bollman, Sheard and Mann,[3] to 3 hours, as noted by

Bloom,[4] Snell, Greene and Rowntree [5] and Barron and Bumstead.[6] Snell, Greene and Rowntree [5] found that in the dog only traces of bilirubin could be detected in the serum 24 hours after ligation of the common duct with the gall-bladder *in situ*; in 48–72 hours the serum contained 2–4 mg. of bilirubin per 100 cc. and bilirubin appeared in the urine. The degree of bilirubinemia increased progressively until the 2nd or 3rd week, remaining rather constant thereafter with slight daily fluctuations. In animals in which cholecystectomy was performed simultaneously with duct ligation, an increase in the serum bilirubin concentration was noted within 30 minutes, rising to 0.3 mg. at the end of 90 minutes, to 2.2 mg. in 4 hours and to 3–5 mg. at the end of 24 hours. It continued to increase steadily during the first weeks, when a transient decrease occurred, followed by a subsequent rise to a rather constant level. The highest concentration reported by Snell, Greene and Rowntree [5] was 13.4 mg. per 100 cc., at the end of 17 days of stasis. Jordan and Greene [7] observed an increase to 13.5 mg. at the end of 9 weeks of complete stasis and, in one instance reported by Salmon,[8] the serum bilirubin rose to 30 mg. per 100 cc. on the 3rd day. The figures reported by the latter, however, are uniformly considerably higher than those noted by other observers.

The influence of the gall-bladder on the development of hyperbilirubinemia following obstruction of the common bile duct has been demonstrated by Mann and Bollman [9] and Snell, Greene and Rowntree,[5] who showed that jaundice increases more rapidly in dogs following cholecystectomy, ligation of the cystic duct or chemically produced cholecystitis. This is explained on the basis of the observation of Rous and McMaster [10] that an intact gall-bladder possesses the ability to concentrate the bile to a marked degree, thereby delaying the development of an increase in intraductal pressure and hepatic injury following ligation of the common duct. Although marked individual variation in the degree of bilirubinemia was exhibited by the animals in the present study, those with gall-bladders did not differ essentially from those in which cholecystectomy or cystic duct ligation had been performed. In two instances, however (Cats 145 and 146), the serum bilirubin concentration was only 0.47 mg. on the 6th day of stasis; this figure is considerably lower than any noted at a similar stage in cholecystectomized animals. The direct van den Bergh reaction was positive in every case in which bilirubin could be detected in the blood.

The highest serum bilirubin concentration in this series was 15.2 mg. per 100 cc. (Cat 154), obtained on the 6th day of stasis. The marked individual variation in the degree of hyperbilirubinemia is apparent from the data present in Charts 1 and 2. No morphological basis for this variability could be observed. The bile duct changes

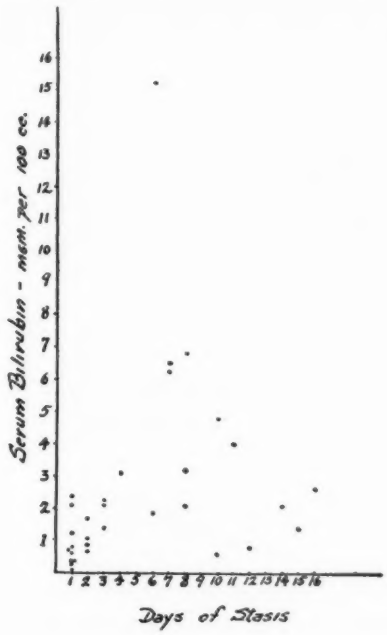

CHART 1

Distribution of serum bilirubin values during total biliary stasis in 15 cholecystectomized cats and 4 with cystic duct ligation.

appeared to progress consistently throughout the experimental period. Sporadic hyaline and nondescript necrosis of hepatic cells varied considerably and seemed to bear no relation to the individual variation in serum bilirubin concentration. The same was true of the focal midzonal areas of necrosis which increased to reach a maximum at the end of about 48 hours and then practically disappeared, being rarely seen in the later stages. Fibrosis about the portal radicles increased steadily with the duration of stasis and became rather promi-

nent at about the time when the serum bilirubin began to fall, but this relation was not constant. The degree of bilirubinemia was also apparently independent of the presence and extent of hepatic cell regeneration in individual cases. However, in the present series, the tendency toward a drop in serum bilirubin approximately coincided with the time of disappearance of mitotic figures from the hepatic cells (10th day). A similar lack of correlation existed with regard to

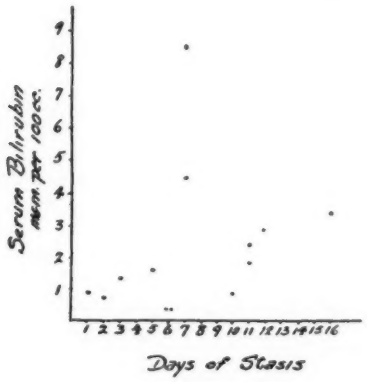

CHART 2

Distribution of serum bilirubin values during total biliary stasis in 10 cats with the gall-bladder *in situ*.

the lipoid content of the hepatic and Kupffer cells, which was studied in detail and will be described in a subsequent communication. These observations seem to indicate that there is no demonstrable correlation, in individual instances, between the changes in the liver and bile ducts and the serum bilirubin concentration at any given time during the period of total bile stasis.

Analysis of the data indicates that, contrary to natural expectation, the serum bilirubin concentration does not tend to increase steadily during the period of stasis. Routine determinations were made at frequent intervals in only 4 animals (Chart 3). In general, the distribution of the serum bilirubin values, as presented in Charts 1 and 2, is in accord with the observation of other investigators that, following ligation of the common duct, the rather rapid initial rise is followed by a fall to a comparatively low level. Snell, Greene and

Rowntree [6] stated that in non-cholecystectomized dogs the degree of bilirubinemia increased progressively until the 2nd or 3rd week and then remained constant, aside from slight daily fluctuations. In cholecystectomized animals the serum bilirubin rose steadily during the 1st week after ligation of the common duct, when a transient decrease occurred, followed in some instances by a secondary rise to the final level. Similar findings were reported by Salmon [8] and by Jordan and Greene.[7]

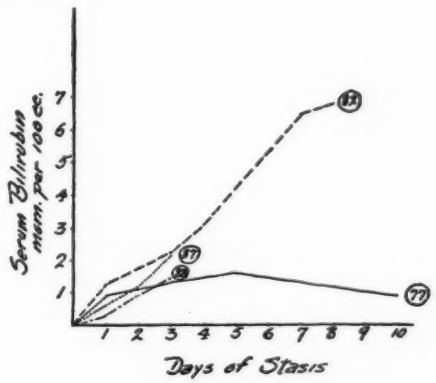

CHART 3

Serial determinations of serum bilirubin concentration during total biliary stasis in 4 cats.

Salmon [8] suggests that this decrease in serum bilirubin concentration may be due to exhaustion of the bilirubin-forming mechanism, the reticulo-endothelial system, associated as it was in his cases with a profound, progressive asthenia. Jordan and Greene [7] discuss in detail the relation between the degree of bilirubinemia and the metabolism of hemoglobin in experimental obstructive jaundice. It has been shown that ligation of the common bile duct of experimental animals is commonly followed by a gradual fall in hemoglobin and the work of Rous and Drury suggests that there is a definite relation between changes in the serum bilirubin concentration and variations in the percentage of hemoglobin. As a result of their studies of anemia in experimental obstructive jaundice, Jordan and Greene [7] concluded that the degree of bilirubinemia seems to vary with the amount of blood being regenerated and with the activity of the me-

tabolism of pigment, rather than with the total amount or percentage of circulating hemoglobin. It appears likely that these factors may be largely responsible for the marked individual variation in the degree of obstructive hyperbilirubinemia noted in the present experiment, as well as in those reported by Snell, Greene and Rowntree,[5] Salmon [8] and Jordan and Greene [7] in dogs, and by Cameron and Oakley [11] in rats. However, the phenomenon of the fall in serum bilirubin following the initial increase appears to be too constant to be dependent upon these exceedingly variable factors. Nor can it be readily explained on the basis of a suddenly increased rate of elimination of bile pigment in the urine for, as reported by Salmon,[8] there is a close parallelism between the blood bilirubin concentration and the renal excretion of bilirubin in dogs with obstructive jaundice. Similarly, Brakefield and Schmidt [12] found that the maximum elimination of bile pigment occurs shortly after the onset of jaundice, the output subsequently declining during the period of continued stasis and reaching a low but somewhat constant level.

There is one factor that has received comparatively little consideration in this connection. Malkoff [13] and Brakefield and Schmidt [12] have shown that when the common bile duct is ligated the bile acid content of the urine increases rapidly and then falls gradually to a comparatively low level. According to the latter, "the output begins to decline about a week after the onset of biliary stasis and finally reaches a value which in some instances is probably within the limits of accuracy of the method employed." The observations of Varela Fuentes, Apolo and Esculies,[14] Snell, Greene and Rowntree [15] and Rowntree, Greene and Aldrich [16] indicate a corresponding change in the bile acid content of the blood. The fact that the time at which the diminution in bile acids occurs approximately coincides with the secondary drop in the serum bilirubin concentration may be of significance. This problem is at present under investigation.

Bromsulphalein Retention

In his original observations, Rosenthal [17] found that abnormal retention of phenoltetrachlorphthalein did not occur during the first 3 days following ligation of the common bile duct. However, Snell, Greene and Rowntree,[5] employing a dosage of 10 mg. per kilogram of body weight (double the clinical dosage), reported beginning

retention in from 48 to 72 hours in non-cholecystectomized dogs and within 24 hours in cholecystectomized dogs. They found that dye retention approximately paralleled the curve of bilirubinemia during the period of stasis. After intensive trial in a large number of cats we found that although bromsulphalein tends to disappear from the blood stream more rapidly than in human beings, nevertheless the

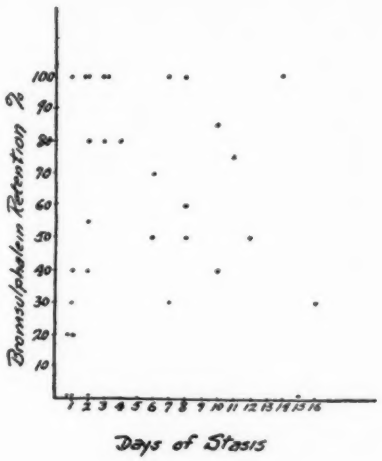

CHART 4

Distribution of bromsulphalein retention values during total biliary stasis in 15 cholecystectomized cats and 4 with cystic duct ligation.

dose employed clinically, 2 mg. per kilogram, was the maximum quantity which would consistently be completely removed from the blood within 30 minutes. Our findings coincide with those of Snell, Greene and Rowntree [5] in so far as the time of appearance of dye retention is concerned. Analysis of our data, however, indicates that contrary to their findings there is no constant relation between the degree of dye retention and the serum bilirubin concentration. Serial determinations made in 5 cases (Chart 6) reveal the same discrepancy. This lack of correlation was most striking in the group of cholecystectomized animals, particularly in the early days of stasis, but it was also present in the non-cholecystectomized group.

If one keeps in mind the fact that much more significance must be attached to high than to low values in these animals, the occurrence

of 100 per cent dye retention on the 1st day of stasis in 1 case (Cat 87), on the 2nd day in 2 cases (Cats 87 and 147) and on the 3rd day in 2 cases (Cats 87 and 88) and of values ranging from 40 to 80 per cent in several others within the first 72 hours, appears noteworthy. The range of individual variation in the degree of dye retention was even more marked than in that of bilirubinemia and was not con-

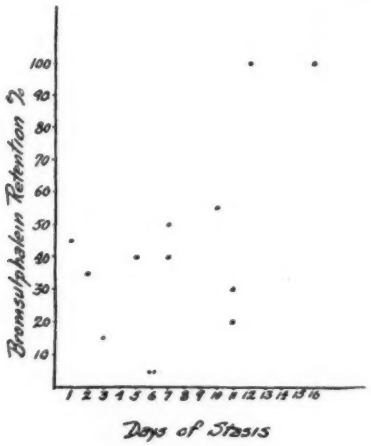

CHART 5

Distribution of bromsulphalein retention values during total biliary stasis in 10 cats with the gall-bladder *in situ*.

sistently related to the duration of stasis in the group as a whole, less so in the cholecystectomized than in the non-cholecystectomized animals (Charts 4 and 5). For example, 100 per cent retention was present in Cats 147, 88, 87, 114, 82, and 125 with stasis of 1 to 15 days duration, with serum bilirubin concentrations of 2.4, 1.4, 0.61, 6.27, 6.8 and 3.4 mg. respectively. As was the case with the serum bilirubin content, there was no apparent relation between the degree of bromsulphalein retention and the morphological changes in the liver and bile ducts, either in individual instances or in the group as a whole. It was noted, however, that the degree of dye retention appeared to parallel the clinical condition of the animal more closely than did any other factor included in the experimental observations. The most marked retention almost invariably occurred in cats that

were obviously quite toxic, although relatively low grades of retention were occasionally observed in such animals.

The immediate marked retention of bromsulphalein which occurred in some cases might conceivably have been due in part to the simultaneous removal of the gall-bladder, as was noted clinically following cholecystectomy by Cantarow, Gartman and Ricchiuti.[18] However, in Cats 87 and 88, which showed 100 per cent retention 24 hours after ligation of the common duct, the cystic duct had been

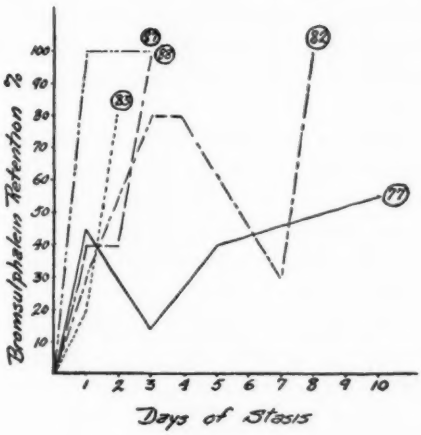

CHART 6

Serial determinations of bromsulphalein retention during total biliary stasis in 5 cats.

ligated 2 months previously. It seems evident that the degree of bromsulphalein retention exhibited by cats with complete common duct obstruction does not depend entirely upon the condition of the hepatic parenchyma or the bile ducts. Snell, Greene and Rowntree[5] suggest the possibility of the accumulation of the dye in the obstructed biliary passages with subsequent reabsorption. However, no dye was found in the bile ducts of their animals, although they had received repeated doses during the period of stasis. On the other hand, it has been noted repeatedly that all dye leaves the blood stream within a few hours, regardless of the state of the liver.

These apparently contradictory observations may be explained on the basis of one of three hypotheses: (1) extrahepatic elimination,

(2) storage, or (3) destruction of the dye. It is well known that relatively small quantities of phenoltetrachlorphthalein and bromsulphalein are excreted by the kidneys of normal animals, but the quantity ordinarily eliminated in this manner is far too small (0.1–1 mg. in 2 hours) to account for the rapid removal of the dye from the blood. The question naturally arises as to whether much more might not be excreted in the urine in the presence of common duct obstruction. In this connection, Snell, Greene and Rowntree [5] found that in general the amount of dye in 2 hour specimens of urine ran parallel to the degree of dye retention in the blood. Although it would appear that this hypothesis is untenable, it cannot be entirely eliminated from consideration on the basis of the limited amount of information now available.

The observations of Fiessinger and Longchampt,[19] Saxl and Donath [20] and Schellong and Eisler [21] suggested that phenoltetrachlorphthalein is removed from the blood by cells of the reticulo-endothelial system and should be regarded as a test of the functional activity of this system rather than of the liver. A similar suggestion was made by Herlitz [22] with regard to bromsulphalein. Klein and Levinson [23] found that splenectomy or reticulo-endothelial blockade with India ink resulted in definite delay in the rate of removal of this dye from the blood, this effect persisting for variable periods of time up to 30 days. They believe that bromsulphalein is excreted through the reticulo-endothelial system, the Kupffer cells playing an important rôle in this connection. Although the degree of dye retention reported by these observers was in most cases relatively slight, no statement can be made with regard to the possible alteration in reticulo-endothelial cell activity in the removal and storage of bromsulphalein in animals with total bile stasis. On the other hand, Rosenthal and Lillie [24] found that splenectomy and reticulo-endothelial blockade with colloidal quartz had no demonstrable effect upon bromsulphalein excretion in rabbits, suggesting that the reticulo-endothelial system plays no part in this process and implying that the polygonal cells of the liver are the elements chiefly concerned in the removal of the dye from the blood. This controversial point requires further investigation.

There is some evidence, both direct and indirect, that members of the phenolphthalein group of compounds may be destroyed in the tissues. Kendall [25] has shown that the disappearance of a portion of

injected phenolsulphonephthalein may be accounted for in this way, and Snell, Greene and Rowntree[5] found that phenoltetrachlorphthalein is rapidly destroyed when incubated with ground liver or muscle tissue. Careful examination of animals with common duct ligation has frequently failed to reveal any evidence of the accumulation of the dye in the tissues in spite of the fact that only small quantities have been eliminated in the urine and little or none may be present in the blood. It seems likely that the existing wide variations in the degree of bromsulphalein retention in cats with total bile stasis may be largely dependent upon a variable rate of destruction of the dye in the tissues, although the possible importance of renal elimination and reticulo-endothelial storage cannot be denied.

Summary and Conclusions

1. Morphological changes in the liver and bile ducts are presented in relation to simultaneous changes in serum bilirubin concentration and bromsulphalein retention in 29 adult cats with uncomplicated total bile stasis produced by ligation of the common duct. The progression and regression of characteristic lesions in the liver and bile ducts are described in detail. The time of appearance of white bile is apparently extremely inconstant.

2. There was a marked degree of individual variation in serum bilirubin concentration. The highest incidence of maximum bilirubinemia in the group as a whole occurred early in the 2nd week of stasis, with a subsequent decline during the remainder of the experimental period (16 days). The time of occurrence of the initial fall in serum bilirubin concentration approximately coincided with the time of disappearance of mitotic figures from the hepatic cells, but this correlation was not consistent in individual cases.

3. There was no demonstrable correlation between the morphological changes and the serum bilirubin concentration at any given time during the period of total bile stasis.

4. The range of individual variation in the degree of bromsulphalein retention was more marked than in that of bilirubinemia and was not consistently related to the duration of stasis or to the serum bilirubin concentration.

5. There was no apparent correlation between the degree of dye retention and the morphological changes in the liver and bile ducts, either in individual instances or in the group as a whole.

6. Anemia, activity of hemoglobin regeneration and suppression of bile acid synthesis are discussed in relation to their possible influence upon the changes in serum bilirubin concentration during total stasis. The observed variations in the degree of bromsulphalein retention may be dependent upon several variable factors, including destruction, storage or extrahepatic elimination of the dye.

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SIDEROTIC NODULES (GANDY-GAMNA BODIES) IN PRIMARY RENAL CARCINOMA *

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Since the first description of siderotic nodules appeared in 1904 (Stengel [1]), these lesions are being observed with increasing frequency in the spleens of individuals presenting a wide variety of clinical conditions. They have also been encountered in the ovary (Henke and Lubarsch,[2] Kraus,[3] Abrikossoff,[4] and Kauder [5]), in hyperplastic thyroid tissue (Schuppisser,[6] and Kraus[3]), in the midbrain (Herzenberg [7]) and retroperitoneal lymph nodes (Schuppisser,[6] Kauder [5]) in cases of hemochromatosis, and in the bladder in a case of acute fulminating hemorrhagic and necrotizing cystitis (Kohly [8]). Their presence in other organs and tissues of the body, aside from the spleen, however, is rarely noted and only one report (Borromeo [9]) of their occurrence in the tissue of primary renal carcinoma could be found in the literature.

DESCRIPTION OF HISTOLOGICAL PREPARATIONS

The sections stained with hematoxylin and eosin consist of an area of kidney with an attached, solid, cellular, encapsulated carcinoma of the so-called hypernephroma type without much stroma or reduplication of cords, alveoli, tubules or cysts (Fig. 1). The renal tissue contains no pigment and shows only anemia with mild parenchymatous degeneration of tubular epithelium, except in the area adjacent to the capsule of the tumor where the atrophic and reactive changes usually observed under these circumstances are present. The cells of the tumor are large, polyhedral and uniform in size with finely and coarsely vacuolated cytoplasm, and regular, small, round, well stained nuclei which are rarely seen in mitosis. They are everywhere supported by a fine reticulum and further separated into sheets and masses by narrow bands and islands of vascular adult connective

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tissue. They are nourished in addition by blood carried in numerous, large, irregular, immature vessels consisting merely of clefts in the tissue lined by tumor cells. Macrophages with foamy or pigmented cytoplasm are occasionally observed engulfing erythrocytes and necrotic tumor cells.

The capsule separating the carcinoma from the renal tissue proper consists of a zone of connective tissue approximately 2 mm. wide and moderately cellular, but with very little pigment on the side toward the renal tissue. The remaining half of the capsule is composed of acellular, wavy collagen fibers arranged in bundles and diffusely impregnated in large patches with amorphous granules and variably sized, small, round, sharply etched bodies 8 to 15 microns in diameter which lake hematoxylin. One corner of the capsule lying against the tumor tissue contains extravasated erythrocytes, carcinoma cells, lymphocytes, many blood vessels and peculiar pigmented lesions (Fig. 1).

The pigment occurs in the form of purple masses and coarse brown granules, and in concentric circular collections of slender, dark blue streaks and greenish, segmented, bamboo-like rods presenting a wreath-like arrangement about the blood vessels, not only in the capsule but also in the tumor tissue proper. In a typical example (Fig. 2) the center consists of a small vessel open to the flow of blood and lined by endothelial cells attached to a narrow wall of collagen material. This is surrounded by a wide, clear, foamy reticulated zone of delicate collagen fibers devoid of iron pigment and staining light blue with Mallory's and faintly red with Van Gieson's connective tissue stains. The outer limits of this zone end abruptly against a thin, wavy, and sometimes linear lamina, pale green in unstained preparations, dark blue with Mallory's potassium ferrocyanide stain and with hematoxylin and eosin, red with the fibroglia and Van Gieson's stains and black with Verhoeff's elastic tissue stain. Occasionally two lamina are present, separated by the interposition of thick, segmented and branched, bamboo-like rods, pale green in unstained preparations, brown and sometimes bluish with Mallory's collagen stain, bluish mustard-brown or brownish red with the fibroglia stain, blue with potassium ferrocyanide, green with hematoxylin and eosin, and greenish, greenish yellow and sometimes reddish with Van Gieson's stain. Although some of the vessels are surrounded exclusively by the bamboo-like rods, in the majority of instances the initial de-

posit of pigment occurs in the form of blue lines, the outer one of which is replaced by thicker, but similarly shaped bands of greenish material which ultimately develops into the bamboo-like rods. Eventually these segmented rods form confluent masses and their edges become progressively irregular and granular, nearing complete disintegration into amorphous débris. Many of the pigment masses are engulfed by foreign body giant cells and broken down in this manner. The giant cells form initially within the zone of foamy reticulated network and occasionally attain enormous proportions, having as many as seventy nuclei in single sections and many more in complete serial sections. As a rule they engulf only the pigment, leaving the thin-walled vessel and its surrounding reticulated zone intact; at other times, however, the whole vessel wall with its pigment and lumen together is engulfed. Within the giant cells the segmented rods and blue lamina are broken down into spicules, small crystals and rounded droplets.

The pigmentation within the tumor tissue proper presents a varied morphology. There are large bars of refractile, reddish brown, iron-free pigment unaffected by any of the staining reactions employed. The outlines of these bars are sharp and often appear freshly fractured; the surface is flat and seems to be constructed of layer upon layer of flat crystalline material resembling somewhat cholesterol plates. Other pigment masses are hyaline in character, stain pink with hematoxylin and eosin, red with Van Gieson's and blue with potassium ferrocyanide and Mallory's collagen stain. These hyaline masses occupy large areas traversed by thin strands of connective tissue and are closely related and sometimes continuous with denser, disk-shaped masses showing flat surfaces of concentric circles, often resembling small concretions (Fig. 3), and which stain an intense blue with potassium ferrocyanide, brown with Mallory's collagen stain and red, yellowish brown or even purple with Van Gieson's stain. The tumor cells in the vicinity of the immature blood spaces contain iron pigment which is found impregnating the chromatin material of the nucleus and which also occurs as small punctate dots or diffuse staining material in the cytoplasm. The reticulum supporting the tumor cells is stippled with fine, iron pigment granules contained within a poorly demarcated zone staining pink with eosin and somewhat orange with the fibroglia stain, and which appears like a neutrophilic smudge with hematoxylin and eosin. This fine, dust-like

pigment coalesces to form larger agminate masses, round or oval, with short projections or fine rosette formation, pale green in unstained preparations, green and sometimes pink with Van Gieson's stain, blue or mustard-brown with the fibroglia stain, and brown, brownish green or blue with Mallory's collagen stain. These masses sometimes seem to form in larger, hyaline, disk-shaped bodies. The smaller particles of pigment are phagocytosed by macrophages and in the larger islands of connective tissue which stud the tumor, there are enormous quantities of pigment (Fig. 4) often within giant cells or free in the form of a coarse feltwork traversed by connective tissue and staining various shades between blue and green in the potassium ferrocyanide preparations and green, brown or purple with hematoxylin and eosin. In these situations the giant cells contain irregular segmented rods with lateral projections and collateral off-shoots which serve to unite several of the masses into a single continuous piece.

Discussion

A purely mechanical origin for the development of siderotic nodules was first postulated by Gandy,[10] who attributed a great deal of importance to vascular stasis, hemorrhage, pigmentation and fibrosis. The relation between incrustations of calcium and iron salts on degenerated tissue fibers has recently been reviewed and discussed at length by Bennett,[11] and Davis and Warren.[12] Other investigators of these lesions have been concerned not only with hypothecating an etiological basis for their development, but also in explaining the microscopic structure, the origin of the associated hemorrhages and the chemical nature of the pigments and other inorganic material of which they are composed. The characteristically shaped, pale green, pigmented rods which resemble mycelial structures are largely composed of iron phosphate (Kraus) deposited on a substratum of elastic tissue and collagen fibers (Glasunow,[13] and Schuppisser[6]). According to Christeller and Puskeppelies [14] the intima and collagenous mural fibers of the smaller splenic arteries undergo degeneration with resulting extensive extravasation of blood which slowly hemolyzes, the liberated pigment becoming incrustated on the previously damaged fibrillar material. Gáspár,[15] however, in agreement with most other observers, believes that in the spleen the lesions are derived from hemorrhages originating mainly in the vicinity of the trabecular

veins, the incrustations of the arterial walls within the area of involvement being secondary manifestations, which occur at first only on the side facing the hemolyzing erythrocytes. Fasiani and Osella-dore [16] effected the development of siderotic nodules experimentally in dogs and cats by ligating the veins at the hilum of the spleen, within which areas of necrosis were then produced by employing various physical and chemical agents such as caustics, diathermy coagulation and intraparenchymatous injections of alcohol and solutions of calcium chloride. Although emphasizing the importance of necrotic lesions in the genesis of these pigmented nodules, these investigators were inclined to support Jäger's [17] view that the nodules can occur as a result of chronic stasis alone. If this were true, however, the conditions present in the neoplastic tissue of primary carcinoma of the kidney would constitute an ideal situation for their development, since the renal vein is frequently partially or completely occluded by proliferating tumor cells, and the occurrence of congestion, hemorrhage and necrosis is the rule. Only one case similar to our own has been reported in the literature (Borromeo [9]). Moreover, we were unable to find siderotic nodules in the histological sections of 62 additional cases of primary renal carcinoma in which, however, rapid cellular division, vascular thrombosis, passive congestion, hemorrhage, areas of necrosis, crystalline lipoidal material and the salts of calcium and iron were present in varying degree and combination. Although changes of this type may occupy an important secondary position in initiating the formation of siderotic nodules, it would appear that the genesis of these lesions depends primarily on the presence of additional factors, the nature of which is incompletely understood at the present time. Furthermore, these stimuli are evidently not operative in situations in which calcification commonly occurs, as for example, old infarcts, sclerotic blood vessels, fibrotic heart valves, areas of caseous necrosis and collections of inspissated pus.

In regard to a possible parasitic origin which has been postulated by Gibson,[18] Nanta, Pinoy and Gruny,[19] Askanazy and Schweizer,[20] and others, McNee [21] believes that in view of the different organisms obtained in the reports just mentioned and in the cases examined by Jaffé and Hill,[22] it would be illogical at present to regard the siderotic nodules as specific lesions resulting from mycotic infection. Cultures were not made in our case but there was no histological evidence in-

dicating the presence of parasitic infection. The statement made by Kohly that the mycelial-like threads in the siderotic nodules of splenic tissue represent multiple fractures of the rod-shaped elements by contractions of that organ does not seem tenable, in view of the fact that in the kidney of our case the segmented appearance was quite characteristic in the absence of any such contractile force.

Summary

A description of siderotic nodules (Gandy-Gamna bodies) occurring in 1 of 63 cases of primary renal carcinoma is given and illustrated.

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DESCRIPTION OF PLATES

PLATE 73

FIG. 1. Encapsulated portion of primary renal carcinoma showing Gandy-Gamna bodies in upper portion of the field. Hematoxylin and eosin stain. × 50.

FIG 2. Capsule of tumor containing a vessel surrounded by a dark wavy line and concentrically arranged, pale, segmented rods. The lumen of the vessel is narrow and is separated from the pigment by a fine reticulated structure containing a few nuclei. Note the presence of pigment in the surrounding tissue. Hematoxylin and eosin stain. About × 400.

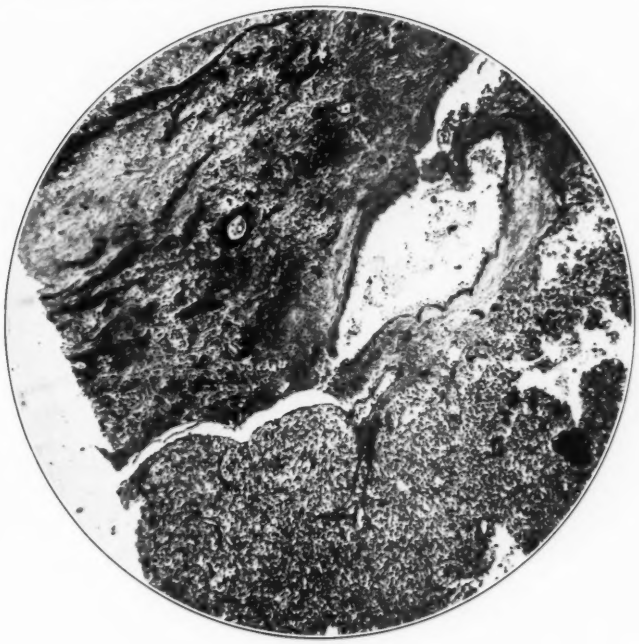

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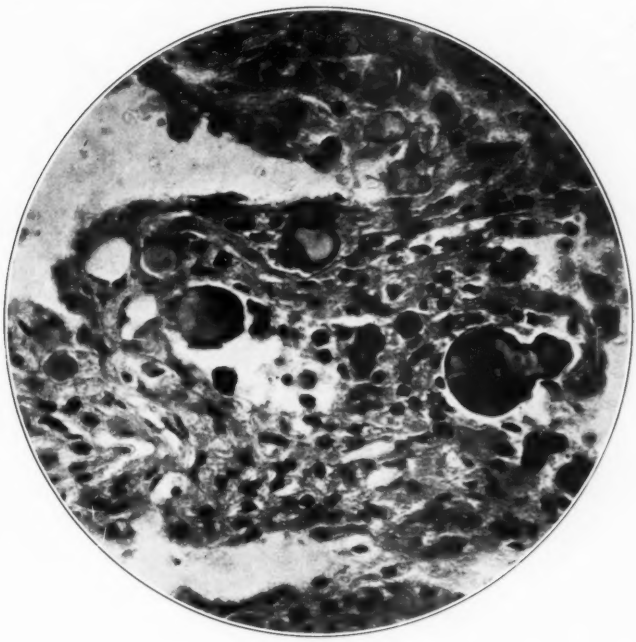
PLATE 74

FIG. 3. Disk-shaped pigment masses resembling small concretions. Hematoxylin and eosin stain. About × 450.

FIG. 4. Island-like collections of pigment within the tumor tissue. Note the foreign body giant cell to the left of the center. Hematoxylin and eosin stain. About × 380.



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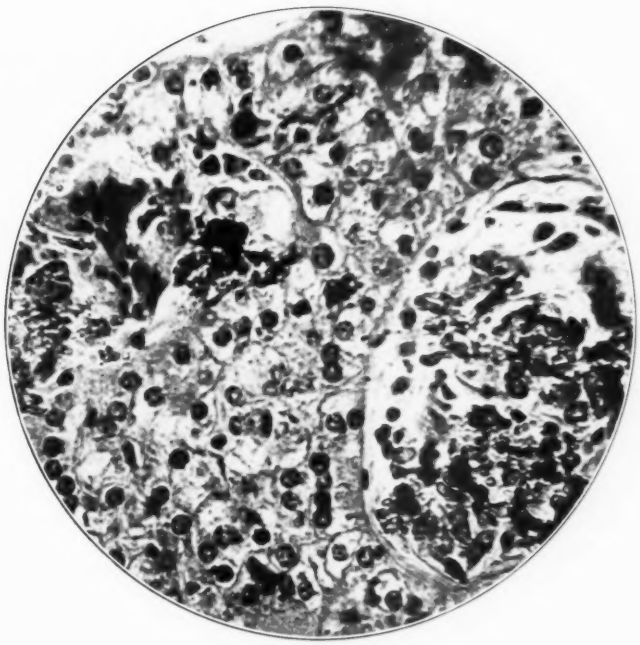

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